REFLEXOGENIC AREAS OF THE CARDIOVASCULAR SYSTEM

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by

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This book is dedicated

to the memory of

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Beloved teachers and great physiologists

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PREFACE

SHORTLY after the discovery by H E Hering in 1924 of the baroreceptor reflex function of the carotid sinus there appeared several monographs on the reflex control of the circulation Notable were those of Hering (1927) Heymans (1929) and Koch (1931) By 1931 the concept of the baroreceptor reflex control of the circulation by the sino aortic areas was reasonably well documented

In 1927 and in 1930-31 Heymans and his colleagues discovered the chemoreceptor function of the aortic and carotid bodies and provided convincing proof of the important reflex effects of these zones on respiration and circulation Shortly afterwards the mono graph of Heymans Bouckaert & Regniers (1933) summarized the role of the baroreceptor and chemoreceptor reflexogenic zones in the control of breathing and circulation Since the appearance of their monograph no book has been written which provided a full discussion of the problems which they considered

The present monograph is not merely an expanded version of that written in 1933 but is an entirely new book In addition to a full discussion of the work done in the last twenty five years on the functional role of the baroreceptor and chemoreceptor sino aortic reflexes much more new material is presented This includes a review of the vascular receptors in the thoracic aorta mesenteric vessels and peripheral vasculature and their function Recent developments in the study of the reflexes from the heart itself and from the lung vessels have resulted in an improved understanding of these important reflexogenic zones The last section of the book deals with a study of the cardio pulmonary reflexes methods ranging from those of classical perfusion to those of electrophysiology are described and the results obtained therefrom discussed Evidence from pharmaco logical studies and from the effects of multiple capillary embolization reveals that the lung vessels are important reflexogenic sites The behaviour of the atrial and ventricular receptors suggests that they subserve functions such as were adumbrated ninety years ago for the depressor nerve endings by Cyon & Ludwig who mistakenly believed that the depressor nerve arose from the heart itself

Although the main bulk of the book is devoted to an account of the physiology of the cardiovascular reflexes considerable attention has been paid to pharmacological effects exerted on these mechanisms and to the role of the reflexes in patho physiological states It is therefore hoped that this book will be of interest not only to physiologists but to pharmacologists and clinicians

We wish to thank our colleagues for permission to publish figures abstracted from their published or unpublished work We are grateful to the following journals for permission to reproduce figures *Acta Anatomica Acta Physiological Scandinavica American Journal of Anatomy American Journal of Physiology Anæsthesiology Archives internationales de Pharmacodynamie Archivio di Italiana di Anatomia e di embriologia Circulation Research Compte rendu hebdomadaire des seances et memoires de la Societe de biologie Journal of Anatomy Journal of Physiology Proceedings of the Society of Experimental Biology and Medicine Quarterly Journal of Experimental Physiology and*

Trabajos del Laboratorio de investigaciones biológicas de la Universidad de Madrid The following publishers have kindly allowed us to use figures from monographs published by them G Doin, of Paris (*Le sinus carotidien* 1933 by Heymans Bouckaert & Regniers) and T Steinkopff of Dresden (*Die Karotissinusreflexe* 1927 by Hering and *Die Reflektorische Selbsteuerung des Kreislaufes* 1931 by Koch)

Our secretaries deserve a heartfelt word of praise for their efforts in transmuting difficult manuscripts into respectable typescript

Lastly we wish to thank the publishers and particularly Mr J Rivers and Mr J A Rivers for every courtesy and help and to congratulate the printers on the excellence of their work

C HEYMANS
E NEIL

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Section 1 The Arterial Baroreceptors

CHAPTER 1

ANATOMY AND HISTOLOGY OF THE ARTERIAL BARORECEPTOR AREAS IN THE MAMMAL

The Carotid Sinus of the Mammalia

THE CAROTID SINUS is a dilation of the internal carotid artery situated at the origin of the vessel (Fig 1)



FIG 1 The right carotid sinus and carotid bifurcation of the dog The tip of the aneurysm needle is introduced under the right internal carotid artery and immediately to the left in the picture the sinus itself is clearly seen The external carotid artery is shown as the larger branch of the bifurcation Between the internal and external carotid arteries can be seen a mass of tissue which includes the carotid body and the sinus nerve The white nerve trunk seen on the right of the picture is the vago-sympathetic nerve —(C Heymans)

The presence of a dilatation in this site had been known to the anatomists for a long time but it seems that the older workers (e g Henle Arnold Luschka & Schwalbe) had not distinguished it in any particular way from the enlargement which is commonly found in vessels at the point of branching or division

L Meyer (1876) seems to have been the first to recognise that the dilatation was associated with a marked thinning of the arterial wall but the very title of his paper—

Über aneurysmatische Veranderungen der Carotis interna bei Geisteskranker —did not suggest that the sinus was a normal structure or for that matter that it occurred in normal people Schafer (1877) however showed that the dilatation was present in normal adult cadavers and Binswanger (1879) confirmed this He distinguished three different sites of the dilatation (*a*) situated exclusively on the internal carotid (*b*) at the bifurcation of the common carotid extending into both branches and (*c*) involving both the bifurcation and the internal carotid artery In 182 cases which he examined 81 belonged to the first, 59 to the third and 42 to the second type Binswanger confirmed the thinning of the arterial wall which he described as beginning sharply at the origin of the internal carotid artery and stated that the thinning was due to the sparsity of muscular tissue in the media He could not find any evidence of the sinus dilatation in infants De Castro (1926 1928) and Hering (1927) have since shown that the structure is present in infants although De Castro found that it could not be recognised in the foetus

With the exception of the ruminants the carotid sinus is present in all other mammalia In the ruminant the origin of the occipital artery is the site of a dense baroreceptor innervation which corresponds to that of the sinus in the other mammals (De Castro 1928)

Knoll (1885) first described as Sinusnerv the branch of the glossopharyngeal nerve which runs to the region of the carotid bifurcation In general however the anatomists of the last century regarded this glossopharyngeal branch as only one of the many nerve twigs which contributed to the intercarotid plexus described by Arnold The vagus and sympathetic contributions to this plexus were so numerous as to overshadow that of the deeper lying sinus nerve Indeed it was only the proof by Hering that the stimulation of the central end of the sinus nerve caused reflex bradycardia and systemic hypotension that focused interest on the details of the innervation of the carotid sinus itself Hering also showed that the vascular reflexes aroused by mechanical stimulation of the sinus wall were entirely abolished by section of the sinus nerve Although Braeucker (1922) and Danielopolu and his co workers (1927) insisted that the vagus sympathetic and glossopharyngeal nerves contributed to the innervation of the sinus this experimental proof of the overwhelming importance of the glossopharyngeal sensory innervation has been widely confirmed

Shortly before the demonstration that the carotid sinus was a reflexogenic area Gerard and Billingsley (1923) had described the innervation of the carotid bifurcation and the adjacent carotid body in cats dogs and men They found in the nerve a great preponderance of small myelinated fibres (2–4μ) and only a few fibres in the 9–12μ range

De Castro (1926 1928) was the first to demonstrate the extraordinary richness of the sensory innervation of the carotid sinus Using silver impregnation methods or the methylene blue technique he shewed that the wall of the sinus was the site of two types of sensory nerve ending Type I were diffuse arborizations and Type II were circumscribed glomerular like structures (Fig 2) Generally speaking the receptors lay between the collagen fibres of the adventitia particularly in its deeper layers parallel to the longitudinal axis of the vessel Sunder Plassmann (1930) also recognized two sets of afferent receptors but called the arborizations of coarse structure Type I and referred to those which showed more diffuse arborization with slender branches which ended in fine terminal nets as Type II There seems no very good reason for differentiating the receptors

in this way particularly as the nomenclature adopted by Sunder Plassmann differs from that already suggested by De Castro The work of Abraham (1941 1949 1953 and 1955) on the histology of this area and its homologue the aortic arch suggests that the terminal fibres of the sinus nerve (or the aortic nerve) are transformed into very variable forms of ending They may be ivy shaped neurofibrillary plates coils or dense latticeworks The important point would seem to be that the sensory innervation is rich De Castro Sunder Plassmann and Abraham all aver that the sensory endings occur only in the

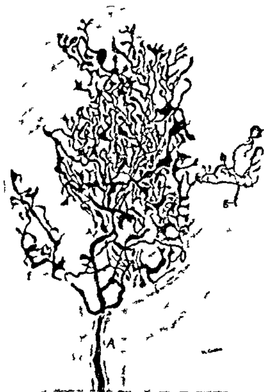


FIG 2 Type II receptor from the sinus wall of an adult man Tangential section magnification × 1050 A = large myelinated nerve fibre g, f = terminal nerve endings —(F De Castro 1928 *Trab Lab Invest biol Univ Madr* 25 331)

adventitia Others (Establе personal communication Rijnders 1933 Ochoterena 1936 Palme 1934 and Meijling 1938) have claimed that some nerve endings may be found in the media

De Castro pointed out that the thinning of the media which so characterizes the wall of the carotid sinus was particularly obvious on the ventromedial surface of the sinus at the point of entrance of the sinus nerve—i e at the very origin of the internal carotid artery (Fig 3) The adventitia in this region is fairly dense The media on the other hand is almost free from muscle fibres but contains a high proportion of elastic fibres Sunder Plassmann (1930) referred to an annular thinning of the media in the wall of the sinus especially just below its equator (see also Addison 1944 1945) Adams (1955) noted that the ventromedial part of the sinus wall near the site of the carotid body is particularly



FIG 3 Sagittal section (slightly oblique) through the carotid bifurcation region of cat embryo (42 mm) Cajal technique
c.e = external carotid *c i* *ci* = internal carotid *c p* = common carotid *n.d* = aortic nerve *l.s* = superior laryngeal nerve *a oc g* = vessel supplying carotid body from the occipital artery *gl car* = carotid body *r a gl* = anastomic branch (third branch) of glossopharyngeal *ni* = sinus nerve *r.simp* = sympathetic branch from superior cervical ganglion *r gl 2* = second branch of glossopharyngeal *gl* = glossopharyngeal nerve *r f v* = pharyngeal branches of nodose ganglion *r d hip* = ramus hypoglossi
Note the rich innervation of the carotid bifurcation derived from the sinus nerve —(F De Castro (1940) *Trab Lab Invest biol Univ Madr* 32 297)

thin in the case of the opossum *Trichosurus vulpecula* and figure 17 of his paper shows beautifully the striking loss of muscularity in the media at this point

Wolhynski (1937) claimed that the sinus wall undergoes a compensatory thickening at the point where it receives the greatest impact of the altered direction of blood flow and suggested that opposite to this the sinus wall became thinner This improbable explanation of the thinness of the ventromedial wall is treated with justifiable scepticism by Adams (1955) who points out that no part of the sinus wall is thicker than that of the internal carotid artery distal to the sinus Adams suggests that the circumscribed thinning of the sinus wall on its ventromedial aspect may be simply developmental in origin being due to the great mesodermal proliferation associated with the formation of the carotid body

opposite this site This may well be so on the other hand Boss & Green (1956) have reported thinning of the media at the site of innervation of various baroreceptor areas scattered along the common carotid artery Here the thinning would simply be referred to the entrance of the nerve fibres as was suggested in the case of the sinus by De Castro

In view of the findings of all other authors it is strange that De Boissezon considers the innervation of the carotid sinus to be hardly superior to that of other vessels (De Boissezon 1942) This author believes however that the baroreceptor function of the carotid bifurcation is subserved by the vessels of the carotid body There is of course no doubt that the vessels supplying the carotid body possess a baroreceptor innervation De Castro himself (1940 1951) has shown this by histological methods and in addition has demonstrated that the electrical stimulation of the nerve endings in the wall of the root of the occipital artery causes reflex cardiovascular effects hardly distinguishable from those evocable by sinus stimulation However Heymans and his co workers Bouckaert & Pannier (1942) have shown that the baroreceptor reflexes arise in the main from the sinus itself whereas the chemoreceptor reflexes take origin from the carotid body If a ligature is tied on the external carotid artery between the occipital artery and the bifurcation then the baroreceptor reflexes can be produced by perfusing the carotid sinus segment whereas little baroreceptor reflex responsiveness exists in the arterial segment rostral to the ligature (Gollwitzer Meier 1934) This disposes of the arguments advanced by De Boissezon which are similar to those previously expressed by Jacobovici Nitzescu and Pop (1928) and Druner (1925)

Lastly it may be conceded that the sympathetic nerves and the pharyngeal vagal branches contribute to the innervation of the carotid sinus and carotid bifurcation Their contribution is of little importance however for section of the sinus nerve invariably abolishes the reflex responses which can normally be evoked by stimulation of the sinus area Hovelacque Maes Binet & Gayet (1930) and Code Dingle & Moorhouse (1936) give details of the innervation of the sinus area in dogs and the first named authors also refer to the anatomy in man (see also Delmas & Laux 1933)

The Common Carotid Baroreceptor Areas

Green (1953 1954) has described a baroreceptor area in the common carotid artery at the level of the superior thyroid artery This area is supplied by a vagal branch which Green named the common carotid nerve This nerve usually emerges from the baroreceptor area close to the origin of the dorsal muscular branch opposite to that of the superior thyroid artery and courses separately from the vagal trunk until it joins the nodose ganglion Occasionally the common carotid nerve joins the aortic nerve or the superior laryngeal nerve The accompanying figure (Fig 4) shows the course of this nerve In addition Green (1954 1956) has described several other sites of baroreceptor endings in the wall of the common carotid artery between the level of the superior thyroid artery and the subclavian bifurcation (Fig 4) These areas are supplied by nerve fibres which join to form the aortic nerve on the right side Similar areas exist on both sides of the neck in the cat Green found these areas by testing all nerve twigs emerging from the wall of the common carotid artery for signs of impulse activity This electroneurographic

method should prove of great use in future investigations of this nature By perfusion of this segment of the carotid Green was able to show that the baroreceptor areas exerted reflex effects on the circulation and respiration similar to those evocable from the carotid sinus and aortic arch

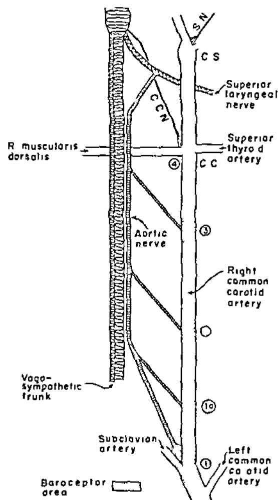


FIG 4 Diagram shows relative positions of baroreceptor areas associated with the cat s right common carotid artery Area 4 (C C) is the common carotid baroreceptor area with its baroreceptor nerve (C C N) and is also present on the left side The nerves from areas 1 1a 2 and 3 form the right aortic (depressor) nerve the left aortic (depressor) arises from the aortic arch C S = carotid sinus baroreceptor area S N = sinus —(J Boss and J H Green (1956) *Circ Research* 4 12)

Boss & Green (1956) reported on the histological features of the arterial wall in these baroreceptor areas The great advantage of these sites is that with the exception of the so called common carotid area the arterial wall structure is not complicated by the presence of branches The nerve fibres tended to enter the arterial wall on one side and then ramified in the inner adventitia the innermost nervous structures being situated immediately next to the outermost part of the media The mass of nervous structures was thus applied to the outer aspect of the media on the side corresponding to the entry of the nervous trunk and such a mass extended around the artery for about one third of its circumference The following characteristics distinguished the arterial walls in these areas (1) there was less muscle in the media (2) the elastic tissue of the media was less corrugated in section (3) there were sometimes fewer elastic laminæ in the media

Baroreceptors of the Aortic Arch

Cyon & Ludwig (1866) believed the depressor nerve described in the rabbit by Thiele (1825) arose from cardiac receptors Roever (1869) Wooldridge (1883) Kazem Beck (1888) and Smirnow (1895) claimed that some endings at least occurred in the aortic arch whereas Koster & Tschermak (1902 1903) localised the receptors in the aortic arch and its immediate thoracic branches and stated that cardiac endings of this nerve were not found (von Schumacher agreed 1902) Tello (1924) showed in mouse embryos that the left aortic (Wooldridge 1883) or depressor nerve endings were confined to the region of the aortic arch The right aortic nerve on the other hand arose from the subclavian carotid angle and the neighbouring part of the brachiocephalic artery In embryos of



FIG 5 Endings of the aortic nerve in the embryo (12 mm) of a white mouse d = Aortic nerve A = Aorta —(J F Tello (1924) *Trab Lab Invest biol Univ Madr* 22 295)

4 mm the fourth branchial arch lay close to the nodose ganglion being almost surrounded by the superior laryngeal nerve At the 12 mm stage the migration of the arch system towards the thorax was accompanied by the appearance of the adult aortic nerve formed from a branch of the superior laryngeal nerve (Stelling 1867 Finkelstein 1880 Sarkar 1922 Perman 1924) The nerve endings were shown to be distributed throughout the circumference of the newly formed aortic arch (Fig 5) For details of the histology of the endings of the depressor see Abraham 1945 1949*b* 1953 1955

In the adult dog cat or rabbit the aortic nerve is most easily located by defining its junction with the superior laryngeal nerve at the angle between the latter and the vagal trunk In the rabbit the aortic nerve is separate in the neck In the cat this is commonly the case although the separate nerve is bound together with the underlying vagus in eine gemeinsame Scheide (Bernhard 1868) Green (1954) has recently shown that baro receptor areas in the common carotid artery are supplied by thin branches from the aortic

nerve The general anatomy of the aortic nerve in the monkey is similar to that in the cat In the dog and in man the aortic nerve, identified by its junction with the superior laryngeal nerve is rarely separate in the neck from the remainder of the vagal fibres

In amphibia the nerve is never separate from the vagal trunk except presumably at its ending in the arterial wall (Nikoforowsky 1912–13 Kuno & Brucke 1914 Neil Strom & Zotterman 1950) In reptiles the nerve passes as a long thin filament throughout the length of the vagus from the region of the heart (Gaskell and Gadow 1883 Mills 1885 Mills & Kronecker 1885)

Tigerstedt (1923) and Koch (1931) should be consulted for literature on the comparative anatomy of the aortic nerves Anufriew (1928) and Schurawlew (1928) give full accounts of the literature in studies on cats and dogs respectively The left depressor nerve commonly leaves the vicinity of the vagus trunk above the annulus of Vieussens and passes behind or just lateral to the left common carotid lying in the lower third of its course anterior to the trachea It reaches the anterior surface of the aortic arch between the origin of the brachiocephalic and left subclavian arteries

For further details of the anatomy of the aortic nerves in mammals see Marmorstein (1929 1933) Marmorstein *et al* (1934) Hirohata & Hashimoto (1936) Velluda has given very full descriptions of the origin and course of the nerves in the rabbit (1927*a*) the dog (1927*b*) and in man (1928–9)

About 450 fibres of which two thirds are myelinated are found in the aortic nerve of the cat (Agostoni *et al* 1957) The myelinated fibres have a bimodal distribution with peaks in the 2–4μ and 8–10μ diameter groups Langley (1892) and Sarkar (1922) found myelinated fibres (4–8μ) in the aortic nerve of the rabbit as well as non myelinated fibres The presence of myelinated afferents (A fibres) and non myelinated afferents (C fibres) was inferred by Douglas Ritchie & Schaumann (1956) from action potential studies of the aortic nerve in the rabbit

CHAPTER 2

COMPARATIVE EMBRYOLOGY AND COMPARATIVE ANATOMY

The Morphology of the Baroreceptor Areas

EBERHARD KOCH (1931) brilliantly interpreted the significance of the anatomical sites of the baroreceptor areas in the mammal He suggested that these sites were those which survived of the embryonic visceral arch vessels and argued that these arch vessels were all provided with corresponding visceral nerves in the embryo Thus the carotid sinus being formed from the IIIrd arch should be innervated by the nerve supplying that arch i e the glossopharyngeal and the aortic arch being formed from the IVth visceral arch vessel should be innervated by a branch of the superior laryngeal nerve He also drew attention to the vagal sensory innervation of the ductus arteriosus—a VIth arch structure

There is now a great deal of positive evidence for Koch s hypothesis derived from studies of comparative anatomy embryology and comparative physiology Before this can be properly appreciated however it is necessary to consider the evolution of the visceral arches in the vertebrates

The primitive chordate animals from which the vertebrates developed were filter feeders Cilia in their buccal cavity and pharynx by their movement created a current of water which entering the mouth passed via the pharynx laterally through gill slits in the sides of the pharynx and the body wall During this passage of water filtering mechanisms in the gill slits strained off plankton and gaseous exchanges occurred in the gill capillaries

With the development of the vertebrates from these simple chordate forms two major changes took place (1) Important modifications occurred in the mouth region as a result the animal was equipped for macro feeding (2) the increase of size resulting from macro feeding was associated with further development of the respiratory function of the gills

In contrast to amphioxus which possesses some 200 visceral clefts the higher vertebrates possess only 4–7 Each cleft develops as a pouch laterally from the pharynx to become continuous with the skin of the body wall Necessarily these clefts divide the mesoderm of the body wall into a series of visceral arches of tissue lying between them The generic terms visceral arch or visceral cleft are strictly accurate Only if the sidewalls of the visceral clefts form respiratory gill filaments however is it correct to speak of them alternatively as gill arches or branchial arches (*branchiæ* = gills) In the Agnatha where no elaborate jaws are found the visceral clefts and arches are seven in number relatively unmodified in structure from that of the more primitive forms However with the evolution of the Gnathostomata the first visceral cleft fuses with the mouth and the skeletal tissue of the first visceral (mandibular) arch is modified to form the jaw skeleton The second visceral arch (hyoid) also becomes modified to give support to the jaw and loses its respiratory functions except in the cartilaginous fishes in which it survives as a small circular opening (the spiracle) with an associated gill like structure

the pseudobranch In bony fish the spiracle may be closed In the Amphibia and Amniota the cleft and skeleton of the hyoid arch contribute to the formation of the middle ear In fish and in Amphibian larvæ the last five visceral clefts develop gills are respiratory in function and are therefore called branchial clefts In the adult Amphibia and the Amniota the fate of the last five visceral clefts is complicated From them arise the thymus parathyroids and the ultimo branchial bodies

Blood Supply of the Visceral Arches

In primitive forms it seems probable that a blood vessel (aortic arch) ran in each visceral arch (caudal to the corresponding visceral cleft) from a median ventral aorta to the lateral dorsal aorta Deoxygenated blood in the ventral aorta could thus be oxygenated in the gill capillaries stemming from the afferent arch vessel and then passed from these capillaries via an efferent arch artery to the dorsal aorta In the Agnatha where there is no complicated jaw apparatus and the visceral clefts are relatively unmodified the arterial arches correspond to the above primitive arrangement But in the dogfish (a *Gnathostome*) only six arterial arches develop Of these the first arterial arch is modified on account of the specialisation of the related mandibular arch and the consequent loss of the spiracular (hyoid) cleft Though the proximal part of the mandibular arterial arch *disappears in all other Gnathostomata in the dogfish the distal portion of the arch persists* as the hyoidean artery The remaining five arterial arches serve as branchial arteries and each comprises afferent and efferent vessels to and from the gills respectively

In the larval frog (tadpole) again the first or mandibular visceral arch is incorporated in the jaw The second or hyoid cleft develops into the middle ear and loses its corres ponding aortic arch The other four visceral clefts (3–6 inclusive) which develop gills possess arterial arches which supply blood to these gills With the development of the adult frog the third arterial arch persists its distal part runs into the dorsal aorta and becomes the internal carotid artery The fourth arch persists as the systemic arch which joins the corresponding vessel on the opposite side to form the dorsal aorta The fifth arch disappears The sixth arch loses its connection with the dorsal aorta and supplies the lung and skin as the pulmo cutaneous arch (see Marshall 1893 Goodrich 1930)

The Mammalia

In the early stage of development of the mammalian embryo there are two primitive aortæ which are continuations of the two endocardial tubes Each of these vessels consists of a short ventral aorta an aortic or visceral arch vessel and a descending aorta Later *the fusion of the cardiac tubes* is accompanied *by the formation of a single truncus* arteriosus or aortic sac from the two ventral aortæ In the mammalian embryo six pairs of aortic arches appear during development but are never present simultaneously (Fig 6) The first two aortic arches are present together stemming from the aortic sac and join the dorsal aortæ with the successive appearance of the third and fourth aortic arches the first and second aortic arches disappear The segment of the dorsal aorta cephalic to the point of junction of the third aortic arch persists as the cranial end of the internal carotid artery The third arch vessel itself forms the common carotid artery from its ventral part and buds off the external carotid artery Distal to the external carotid bud the dorsal part of the third aortic arch forms the origin of the internal carotid artery

Meanwhile the fifth and sixth aortic arch vessels stem out from the aortic sac to join the dorsal aortæ. The fifth, like "a walking shadow, a poor player which struts and frets his hour upon the stage and then is heard no more", rapidly disappears. The sixth arch vessels each give off a descending branch to the developing lung bud. Development of the spiral bulbar septum into the aortic sac causes diversion of blood from the right ventricle into the sixth arch vessels, whereas blood from the left ventricle is pumped into the third and fourth arches.

The dorsal aorta between the junction of the third and fourth aortic arches degenerates in most Amniota (Sphenodon and many Lacertilia provide exceptions to this statement). This segment of the dorsal aorta is known as the ductus caroticus; its disappearance may

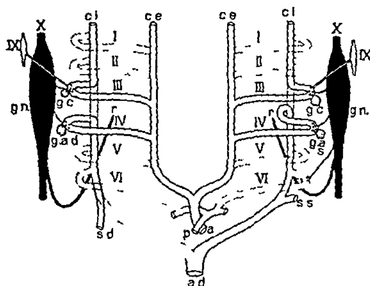


FIG 6. Scheme of the innervation of the aortic arches in the mammal.
X = vagus nerve; IX = glossopharyngeal nerve; c i = internal carotid; c e = external carotid; g c = carotid glomus; g a d = right aortic body; g a s = left aortic body; r = recurrent laryngeal nerve; s s = left subclavian; s d = right subclavian; a d = dorsal aorta; I II III IV V VI = embryonic aortic arches; a = aortic arch; p = pulmonary artery; g n = nodose ganglion of vagus.—(G. Muratori (1937) *Arch. Ital. Anat.* 38, 387)

be related to the increasing encephalisation of higher forms and to the caudal migration of the heart which also accompanies the appearance of the embryonic neck (see Hamilton *et al.* 1952; Arey 1942).

The right dorsal aorta undergoes important changes in mammalia. The segment between its junction with the fourth right aortic arch and its junction with the left dorsal aorta disappears. The right sixth aortic arch henceforth supplies only the developing lung bud and becomes the right pulmonary artery. The left dorsal aorta still makes connection with the sixth left aortic arch; that part of the sixth left arch between the left pulmonary artery and the left dorsal aorta persists until birth as the ductus arteriosus of Botallo (Fig. 7).

The left horn of the aortic sac and the left fourth aortic arch form the aortic arch

of the adult The right horn of the aortic arch elongates, forming the innominate artery which terminates by giving origin to the right common carotid artery (third arch vessel) and the origin of the right subclavian artery (fourth arch) The left subclavian artery arises from the left dorsal aorta near its junction with the left fourth arch vessel

Initially in the early embryo the nerves of the visceral clefts pass lateral to the dorsal aorta to their destination in the visceral arches and then course medially anterior to the corresponding arch artery The mandibular hyoid and carotid arches (Ist IInd IIIrd) are thus supplied by the Vth VIIth and IXth nerves respectively which all lie lateral to the surviving part of the dorsal aorta represented by the internal carotid artery of the adult The nerve of the fourth arch (superior laryngeal branch of the vagus) lies medially to the internal carotid and carotid sinus in the adult however because the ductus caroticus

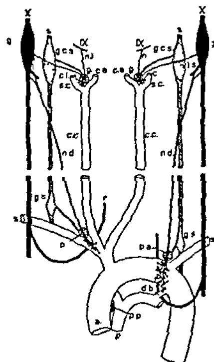


FIG 7 Scheme of innervation of the receptor areas in the aortic and sinus regions in the adult rabbit
X = vagus s = sympathetic g c s = superior cervical ganglion g n = nodose ganglion l s = superior laryngeal nerve g = carotid glomus n i = sinus nerve c.i = internal carotid artery a = aorta c e = external carotid artery p = pulmonary artery IX = glossopharyngeal nerve c c = common carotid artery n d = depressor (aortic) nerve g s = stellate ganglion s c = carotid sinus p p = pulmonary paraganglion p a = aortic paraganglion r = recurrent laryngeal nerve d b = ductus Botalli —(G Muratori (1937) *Arch Ital Anat* 38 387)

has disappeared *It could only remain lateral (i e superficial) to the internal carotid* artery if the ductus caroticus were to persist W E Adams (personal communication) has drawn attention to this point in criticising Figure 3 (after Kreidmann 1878) in the earlier monograph of Heymans Bouckaert & Regniers (1933)

As Boyd (1952*a*) has pointed out the VIth arch nerves are caudal to the corresponding VIth aortic arch vessels and are prevented from slipping forwards as the neck elongates However when the right homologue of the ductus arteriosus disappears the nerve of this side (the recurrent laryngeal) moves cranially to gain a relation with the origin of the next arch (the root of the right subclavian artery) as it loops round the vessel and passes to its distribution in the larynx This cephalic migration is prevented on the left side by the

persisting ductus arteriosus (which becomes the ligamentum arteriosum of the adult) and the left recurrent laryngeal nerve passes round this structure to course headwards to the larynx

Comparative Anatomy and Physiology of the Baroreceptor Areas

Fish

(*a*) **Elasmobranch** Lutz (1930) and Lutz & Wyman (1932*a* *b* *c*) first showed that a rise of pressure in the branchial arches of the dogfish caused cardiac inhibition and a fall of the systemic blood pressure The smooth dogfish (*Mustelus canis*) and the spiny dogfish (*Squalus acanthias*) both possess five true branchial nerves The first branchial nerve is a branch of the glossopharyngeal nerve and the remaining four are branches of the vagus Each branchial nerve divides into three branches pretrematic pharyngeal and post trematic These traverse the floor of the anterior coronary sinus Lutz & Wyman (1932) showed that the stimulation of the central ends of the 1st–4th branchial nerves caused reflex cardiac inhibition Irving Solandt & Solandt (1935) recorded spontaneous impulse activity from the afferent fibres in the pre and post trematic branches of the branchial nerves Normally the systolic pressure in the ventral aorta was about 28 mm Hg and the pulse pressure was about 13 mm Hg On raising the mean pressure in the branchial arches from 15 mm Hg to 25mm Hg increased impulse activity occurred in the afferent nerves which suggested that these nerve fibres functioned in part at least as *baroreceptors*

Boyd (1936) examined nerve endings in the branchial arches of Mustelus having impregnated them with silver Afferent nerve endings were found in relation to the adventitia of the branchial arteries The afferent branches terminated as free nerve endings He suggested that these structures initiated the impulse activity recorded by Irving *et al*

(*b*) **Teleost** McWilliam (1885) noted that mechanical stimulation of the gill itself or of the branchial nerves caused cardiac inhibition Mott (1951) who described the vascular anatomy of the eel in detail (1950) has lately succeeded in demonstrating reflex cardiac inhibition and systemic hypotension by raising the pressure in the isolated inner vated first pair of branchial arches With one exception she was unable to record spontaneous action potentials from the branchial nerves in the resting circulation but reasonably ascribed this failure to the poor state of the venous return On raising the pressure artificially in the ventral aorta an outburst of impulses occurred

Amphibia

(*a*) **Frog** Carman (1955) cites the following description by Marshall (1893) in the tadpole of *Rana temporaria* the branchial circulation is typically that of a gill breather in each arch an afferent vessel from the truncus lies immediately caudal to the efferent vessel going to the dorsal aorta the two being joined at first only by the gill capillaries (Fig 8A) later (12 mm stage) they become connected more directly ventrally to the capillary loops by a small channel (Fig 8B) which so enlarges at metamorphosis that blood from the heart can now pass directly to the dorsal aorta through the efferent vessel the gills receiving less and less blood as the pulmonary circulation is established (Fig 8C) Each external carotid anlage arises (9 mm stage) in the floor of the mouth as

a short blind lumen (Fig 8A) whose posterior end soon turns outwards and dorsally towards *the ventral end of the efferent vessel of the first arch which it joins (12 mm stage)* the two then forming one continuous vessel It is near this junction that the communication between the afferent and efferent vessels occurs This communication at first small and single later becomes plexiform with three or four openings into each vessel and from this plexus the definitive carotid labyrinth develops

The carotid labyrinth (= carotid gland) was first described by Huschke (1831) Its function has long been a subject of discussion Hyrtl (1838) and independently Sabatier (1873) concluded that the organ functioned as an accessory heart and Boas (1882 1883)

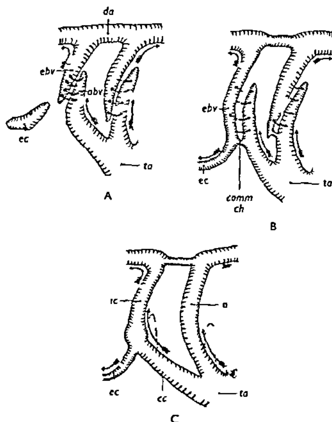


Fig 8 Schematic drawings illustrating the development of the external carotid and the *vascular changes in the first and second* branchial arches at metamorphosis (after Marshall and Pischinger) A 9 mm. stage B 12 mm stage just before metamorphosis C just after metamorphosis Gill capillary loops are represented by broken arrows and the direction of blood flow is shown by continuous arrows—
a = aorta
da = dorsal aorta
ebv = efferent branchial vessel
ec = external carotid
cc = common carotid
ta = truncus arteriosus
abv = afferent branchial vessel
ic = internal carotid
comm ch = communicating channel—
(J B Carman (1956) *J Anat* 89 503)

concurred Others have suggested that it is a chemoreceptor organ on the grounds that the organ contains cells similar to those seen in the mammalian carotid body (De Boissezon 1939, Choudhary 1951) Its site at the cephalic end of the common carotid artery forming a swelling on the internal carotid origin *leads one to suspect that it might* be the homologue of the carotid sinus Palme (1934) has shown the organ to contain sensory nerve endings and Meyer (1927) demonstrated depressor fibres in the glosso pharyngeal nerve which entered the main trunk in the vicinity of the great vessels and also demonstrated that the systemic blood pressure rose when both IXth nerves were cut He did not however state that the depressor nerves arose from the labyrinth itself

Stimulation of these fibres caused a reflex fall of blood pressure. Neil Strom & Zotterman (1950) succeeded in dissecting a long thin nerve which seemed to arise from the carotid gland and from the adjacent part of the common carotid artery (see Fig 1 of their paper) and ran headwards to join the glossopharyngeal nerve. Carman (1955) found a similar nerve in *Hyla aurea* (a common frog in New Zealand). Neil *et al* showed that the nerve endings could be activated by stretch of the blood vessels produced by increasing the stroke volume of the heart. They concluded that this region represented an early development of the mechanism seen in the mammal. They did not claim that the nerve endings were tonically excited as the circulatory conditions in their preparations were necessarily poor following the prolonged dissections entailed. Neither did they state that the nerve endings concerned arose only from the carotid gland. Indeed they mentioned that the nerve fibres seemed to originate central to the position of the gland itself in some cases from the origin of the internal carotid artery. However their cautious claims have since been summarily dealt with by Carman (1955) in his excellent paper. As he points out the structural complexity of the carotid gland itself is such as to suggest that it serves more than baro or chemo receptor functions. He suggests that the labyrinth develops at metamorphosis to ensure that the external carotid artery receives an adequate supply of blood at a reasonable pressure because this vessel develops at an acute angle with its parent vessel—the common carotid—and is therefore hydrodynamically at a disadvantage. His paper contains cogent arguments in support of this belief. Be this as it may his comment that the nerve impulses which were recorded from the origin of the internal carotid artery may well have been pain impulses can be most heartily refuted. There is no doubt whatever that they were recorded from stretch or distortion receptors.

Although Nikiforowsky (1913) claimed that there were depressor afferents in the Xth cranial nerve of the frog his evidence was unconvincing. Kuno & Brucke (1914) showed clearly that electrical stimulation of the central end of the cut vagus caused a reflex fall of blood pressure. Neil Strom & Zotterman (1950) searched in vain for vagal nerve fibres which arose from the main divisions of the truncus arteriosus. The only vagal branch which bears any close relationship to this structure is the laryngeal branch of X. This was considered suggestive remembering that the depressor nerve fibres of the mammal though having their cell bodies in the nodose ganglion of the vagus enter the superior laryngeal division of that nerve. Nevertheless no nerve fibres were found passing from the laryngeal vagal branch to the truncus or to the aorta. It is possible of course that the afferent fibres stimulated electrically by Kuno and Brucke did not arise from the aorta; it is quite conceivable that they arose from the heart itself. Thus Neil and Zotterman have shown that cardiac vagal afferent fibres arise from the atria analogous to those found in the mammal. In the mammal these fibres when stimulated cause brady cardia and systemic hypotension. Kuno and Brucke however showed also that a rise of aortic pressure caused a fall of systemic pressure and bradycardia so there must be some sensory innervation of the truncus which has not yet been found.

(*b*) **Necturus** Lutz & Wyman (1932*c*) succeeded in evoking cardiovascular reflexes in the newt by baroreceptor stimulation.

Amniotes

(*a*) **Reptiles** Boyd (1941) studied the innervation of the carotid region in *Vipera*

berus The Ophidia are highly specialized showing a wide separation of the IIIrd and IVth arches and a disappearance of one common carotid artery The blood supply to the carotid system arises from the right systemic arch artery by a single trunk which after giving a branch to the thyroid runs behind the thymus to the left continuing anteriorly as the left common carotid artery Near the head this artery divides into the left internal and external carotid arteries The right carotid system receives its blood supply by way of a transverse anastomosis The origin of the internal carotid artery shows a slight dilatation and a thickened cuff of adventitial connective tissue There are ramifying nerve fibres in the adventitial wall but these afferent fibres show only slight branching The nerve fibres are derived from the vagus but Boyd points out that this is probably due to the assimilation of IXth fibres in the upper part of the vagus trunk Boyd regards the dilatation at the commencement of the internal carotid as the homologue of the mammalian carotid sinus Adams (1952) has described the anatomy and histology of the termination of the common carotid artery and the commencement of the internal carotid together with the adjacent carotid body in the lizard *Varanus varius* The remarkable feature of the carotid sinus complex is the arrangement at the bifurcation of the common carotid artery whereby the vessel becomes subdivided for a short part of its course into a main and a collateral channel these two channels communicate by a series of separate orifices—Van Bemmelen (1886) has compared the structure in this vicinity in other reptiles (*Lacerta*) with the carotid labyrinth of the frog (see also Palme 1934) Adams found a slender branch of the glossopharyngeal nerve which ran caudally along the ventral aspect of the internal carotid artery and gave off terminal twigs which supplied both sides of the bifurcation At least one of the terminal twigs pierced the adventitia on the medial side between the main and collateral channels Both the main and collateral channels of the carotid bifurcation showed eccentric thinning of the media Adams (1955) has examined the carotid arch in five species of lizards from three families The internal carotid artery never arose by less than two openings whether the species of lizard was one in which the ductus caroticus persisted or not The adventitia in the region of the origin of the internal carotid showed a rich innervation from the superior laryngeal branch of the vagus and contained epithelioid cell nests which Adams regards as the homologue of the glomus caroticum Both these papers give a valuable survey of the literature

Gaskell & Gadow (1885) Mills & Kronecker (1885) and Kazem Beck (1888) studied the anatomy and function of the aortic nerve in the tortoise

(*b*) **Birds** Terni (1927 1931) Muratori (1931 1932 1933 1937) and Schneider (1950 1951) have examined the vaso sensory innervation in birds The carotid bifurcation is not the site of sensory endings The homologue of the carotid sinus and carotid glomus is in the thorax at the origin of the common carotid artery immediately rostral to the root of the subclavian artery in the vicinity of the ultimobranchial body The neighbouring vagus gives numerous nerve branches to supply these structures although Terni states that the prevertebral precarotid branch of the glossopharyngeal nerve supplies the carotid body if not the baroreceptor area The systemic arch of the aorta (IVth arch) which persists on the right in birds is innervated by vagal branches and histology shows typical baroreceptor endings The so called aortic nerve is short owing to the nearness of the nodose ganglion to the aortic arch (von Schumacher 1902) (see figure 12 of Muratori s paper 1937)

Van der Linden (1934) showed that occlusion of both common carotid arteries in the neck caused systemic hypertension but found that this response was due to cerebral anaemia Sinus reflexes played no part because the site of application of the clips was rostral to that of the carotid baroreceptor innervation Stimulation of the carotid bifurcation caused no cardiovascular effects as might be expected from the above anatomical description On the other hand electrical stimulation of the carotid glomus or of the carotid sinus in the thorax yielded variable and unconvincing results Ara (1934) obtained sinus reflex responses by occluding the common carotid artery caudal to the site of the baroreceptors

CHAPTER 3

VASOMOTOR EFFECTS ON THE CIRCULATION AND THEIR REFLEX CONTROL

Vasomotor Effects on Circulation

POUR bien comprendre une Science il faut en connaitre l histoire wrote Auguste Comte In the middle of the nineteenth century great advances were made in our knowledge of some of the factors responsible for the nervous control of the circulation E H Weber (1831) is credited with the proposition that the calibre of the peripheral arteries was affected by nervous influences He based his view on the changes of colour in the skin produced by emotional upsets Henle (1840 1841) demonstrated the wealth of smooth muscle fibres in the media of the small arteries and the vasomotor nerves were christened by Stilling (1840) before there was any clear evidence of the function they were presumed to serve Claude Bernard (1851) found that excision of the superior *cervical ganglion or the section of the cervical sympathetic trunk caused a raised tempera*ture and flushing of the homolateral ear and face of a rabbit At the time he was repeating an old experiment of Pourfour du Petit (1727) who had shown that sympathetic section caused pupillary constriction and conjunctival vasodilatation Bernard made a second report to the Academy of Sciences in 1852 and his attention was directed more to the change in temperature of the affected part than to the vascular changes Indeed he did not think that the rise in temperature was fully accounted for by the increased circulation because it was more persistent than the dilatation of the larger vessels Brown Sequard however was firmly of the opinion that the changes of temperature were merely secondary to the hyperæmia Brown Sequard reported that stimulation of the cut peripheral end of the cervical sympathetic trunk caused vasoconstriction and a fall of skin temperature two months after his arrival in Philadelphia (1852) Bernard reported this same experimental result in December 1853 in his paper on the great sympathetic nerve The same conclusion was arrived at independently by Waller (1853)

Budge (1853) induced vasodilatation by the unilateral extirpation of the spinal cord between the last cervical segment and the third thoracic segment Bernard noted that spinal transection in the cervical region caused a profound fall of blood pressure Goltz *(1864) showed that there were spinal centres responsible for some degree of vaso*constriction Thus the vascular tone in the frog was not entirely lost even when the whole brain was removed but was abolished by the subsequent destruction of the spinal cord Ludwig s pupil Dittmar (1870) was the first to localise the vasomotor centre Excitation of the central end of the sciatic nerve still caused a reflex rise of blood pressure even after transection of the brain stem at the level of the corpora quadrigemina The response however disappeared when the medulla was destroyed Owsjannikow in the same laboratory (1871) localised the centre more accurately by making progressive transverse sections of the brain stem from the collicular level downwards No fall of systemic blood

pressure occurred until the section involved structures lying some 2-3 mm below the colliculi Subsequent sections caused further falls of blood pressure until a maximal effect was evoked by transection at a level 4 mm above the tip of the calamus scriptorius (Cyon 1871) Dittmar (1873) obtained a rise of systemic blood pressure by stimulating the central end of the sciatic nerve even after the grey matter and the posterior columns of the spinal cord were destroyed He concluded that the vasomotor centre discharged over nerve pathways which coursed in the antero lateral columns of the cord

The importance of the splanchnic nerves in the maintenance of peripheral resistance was understood following the proof of their vasoconstrictor function by Ludwig & Thiry (1864) and Cyon & Ludwig (1866) (See McDowall 1935c and 1938 for literature)

According to Franklin (1937) the first use of the term venous tone was that in Richard Lower s De Corde ' (1669) Lower used the phrase relaxato venarum tono in a discussion of the effect of venous dilatation on the heart beat Lower recognized that venous dilatation such as would be produced by the assumption of the erect posture must reduce the inflow of blood to the heart As Franklin has said it took two hundred years for anything fundamental to be added to his statement and the addition was made by Goltz who introduced the idea of a nervous control of venous tonus Goltz (1863) showed that mechanical stimulation of the intestines caused a sixteenfold increase in the contents of the intestinal veins the resulting failure of venous return led to cerebral anæmia and unconsciousness Providing the spinal cord were intact however the veins recovered their tone and the circulation was restored From these Klopfversuch experiments Goltz showed that the tone of veins was dependent on nervous centres in the spinal cord (1864) and medulla he inferred that the sympathetic was the efferent supply to the veins Hooker (1918) was the first to demonstrate the dependence of venous tone on the sympathetic nerves in the mammal (see also Donegan 1921)

Reflex Control of the Circulation

The first idea of a reflex regulation of the cardiovascular system exercised via afferent nerve endings situated in the heart and blood vessels came with the discovery of the depressor nerve by Cyon & Ludwig (1866) They found that the stimulation of the central end of the nerve which lies adjacent to but separate from the vagosympathetic trunks in the neck of the rabbit caused marked bradycardia and systemic hypotension It was later shown that the reflex hypotension still occurred when reflex bradycardia was abolished by atropinisation Cyon and Ludwig believed that the depressor (aortic) nerve arose from endings in the heart itself and considered that these sensory endings were normally responsive to changes in intracardiac pressure If the heart beat too strongly they concluded that reflex bradycardia and systemic hypotension would reduce the work of the heart We know now that the aortic depressor nerve endings are located in the aortic arch and the roots of the great vessels Nevertheless it is curious that within two years of the discovery of the depressor nerve reflexes von Bezold & Hirt (1868) described the reflex bradycardia and systemic hypotension caused by the injection of veratrine 90 years later Paintal (1955) has recently shown that veratrine excites cardiac receptors which appear to serve a function such as Cyon & Ludwig described

Cyon & Ludwig s results in the rabbit were confirmed by Stelling (1867) and extended in cats by Bernhard (1868) Aubert & Roever (1868) Kowalewsky & Adamük (1868)

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in dogs by Roever (1869) Langenbacher (1877) Kreidmann (1878) Finkelstein (1880) Cyon (1898) and François-Franck (1899) in horses by Bernhard (1868) in pigs by Langenbacher (1877) and in guinea pigs by Harrington (1898) Similar results were obtained using non mammalian forms

It is interesting to note that Cyon & Ludwig (1866) did not believe that the aortic depressor nerves were tonically active They found that bilateral section of these nerves did not alter the systemic blood pressure level Sewall & Steiner (1885) later contested this although very respectfully! They claimed that the systemic blood pressure rose by 1-3 cm Hg after cutting both nerves They also confirmed the earlier claim of Nawalichin (1870) that clamping the common carotid arteries caused a rise of systemic blood pressure (this had been previously pointed out by Cooper (1836) and Magendie (1838)) but noted that the rise of blood pressure was much greater if the depressor nerves had been previously cut Nawalichin himself had cut the vago sympathetic nerves at the outset of his experiments These results puzzled Sewall and Steiner who of course ascribed the effects of carotid occlusion on the blood pressure to asphyxial stimulation of the vasomotor centre But if they did not know the mechanism of the sinus reflex they fully appreciated the mode of action of the depressor nerves supposing the normal irritant of the depressor nerve to be the mechanical strain of the contracting heart muscle this irritation would be intensified with every increase of arterial pressure which itself is under the control of the vasomotor centre One of the principal physiological excitants of the centre is a diminution of blood pressure in the brain When therefore the carotids are clamped the vasomotor centre is stimulated, and this of itself would cause general vascular constriction and elevation of blood pressure, but the heart feels this increased resistance to its action in its first beginnings and by means of afferent impulses proceeding along the depressor nerves the action of the vasomotor centre is inhibited

Koster & Tschermak (1902) by degeneration experiments proved that the aortic nerve arose mainly from the aortic arch and the roots of the great vessels and had its cell bodies in the jugular vagal ganglion They demonstrated that action potentials were aroused in the nerve by the distension of the isolated aorta with saline (1903) Einthoven (1908) showed that electrical activity in the aortic nerve occurred with every heart beat Eyster & Hooker (1907 1908) caused bradycardia in animals by distending an isolated innervated segment of the aortic arch Similar reflex responses were reported by Daly & Verney (1926) and Sutton & Lueth (1930)

Reflexes from the Cardio-Aortic Area

Heymans & Ladon (1924, 1925) used a donor dog (A) to perfuse the head of a recipient dog (B) The cephalic ends of the common carotid arteries of dog (B) were anastomosed to the cardiac ends of the common carotid arteries of dog (A) The jugular veins of the two dogs were similarly anastomosed using Payr cannulæ The head of dog (B) was completely separated from its trunk except for the vagi (Fig *9a*) When a rise of pressure was induced in the trunk of (B) by any suitable means (e g an injection of adrenaline) there ensued bradycardia (Fig *9b*) This was reflex for the effect could no longer be obtained after vagal section Conversely if the vagi were intact a fall of systemic pressure in dog (B) caused reflex tachycardia

Anrep & Starling (1925) used the innervated heart lung preparation, in which the head perfused by the H-L was connected to the trunk by the vagi The heart was thus kept under vagal restraint They could not find any evidence of reflex changes of heart rate which occurred when the aortic pressure was raised Later however Anrep & Segall (1926a) were more successful and confirmed the results of Heymans & Ladon

I de Burgh Daly & Verney (1926) showed that a rise of aortic pressure caused brady cardia the technique employed did not allow them to state whether the afferent endings responsible for the initiation of the reflex were restricted to the aorta or whether some lay in the heart itself The same authors (1927) succeeded in showing that both the left

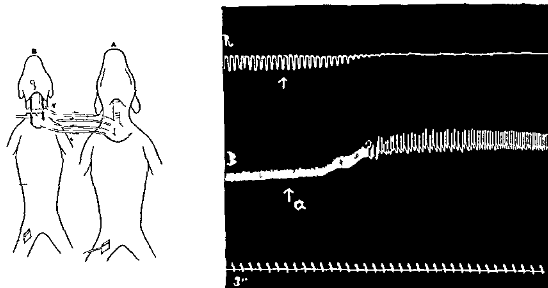


FIG 9 Donor dog A perfuses the isolated head of recipient dog B Head of B attached to its trunk solely by the vagus nerves (see text) (Heymans) Records from above downwards respiratory movements of larynx (R) of isolated head systemic pressure of trunk of B time in three second intervals At a injection of 0 1 mg adrenaline intravenously into trunk of B Systemic hyper tension and marked reflex bradycardia and apnoea —(C Heymans and A Ladon (1925) *Arch int Pharmacodyn* 30 415)

ventricle and the aortic arch were the site of afferent endings excited by a rise of pressure when these endings were suitably stimulated reflex bradycardia occurred

Kahn (1930) used a sound passed down the brachiocephalic artery to dilate the origin of the vessel at its junction with the aortic arch Distension of this part of the brachio cephalic artery caused reflex hypotension

Anrep & Starling (1925) showed that a rise of pressure in the heart and aorta caused vasodilatation of the cephalic vessels The head of a dog (B) was separately perfused by a heart lung preparation made from another dog (A) The trunk of (B) was supplied by its natural circulation By clamping the lower thoracic aorta the cardio aortic pressure was artificially raised in the trunk of (B) The blood pressure in the perfused head fell Section of the vagus nerves abolished these responses This was the first indisputable evidence of the vaso regulatory function of the cardio aortic nerves

Heymans & Bouckaert (1929) confirmed these results using a slightly different tech nique The head of a recipient dog (B) was separated from its trunk except for the spinal cord and the vago sympathetic nerves and was perfused by a donor dog (A) in a manner similar to that previously described The vessels in the thorax of dog (B) were exposed and the brachiocephalic and subclavian arteries were ligatured The pressure in the cephalic vessels of (B) and the femoral arterial blood pressure of (B) were recorded simultaneously A rise of aortic pressure (effected by clamping the descending thoracic aorta) caused a vasodilatation of the cephalic vessels It is likely that this vasodilatation occurred in the extra cerebral blood vessels rather than in those supplying the brain itself

Reflexes from the Right Subclavian Area

The reflexogenic properties of the right subclavian area have been recently studied in the cat by Neil (1956) It will be remembered that Tello (1924) showed that the right aortic nerve in the mouse ends in the angle between the root of the right subclavian and right common carotid arteries Similar findings have been reported for the other mammalia (Nonidez 1935) The experimental study of the reflexogenic properties of this area was undertaken in order to assess the quantitative importance of the cardio vascular responses aroused

The right subclavian artery was tied distally beyond the origin of the thyrocervical axis The thyrocervical costocervical internal mammary and vertebral branches of the right subclavian were tied The right common carotid artery was carefully isolated distal to the superior thyroid branch The superior thyroid artery and the dorsal muscular branch which arises opposite were both ligated The left subclavian was anastomosed to the cephalic end of the left common carotid artery Artificial ventilation was instituted and the chest was opened by a small incision in the second right intercostal space The brachiocephalic artery was ligated proximal to the origin of the carotid and right sub clavian arteries Thereafter the cerebral blood supply was provided entirely by the left subclavian artery which supplied blood via its vertebral branch and via its anastomosis to the left common carotid artery The chest was closed and the pneumo thorax was reduced whereupon the animal breathed normally The right subclavian-carotid segment was either perfused by means of a conventional pump device or was subjected to rises of static pressure Only three successful preparations were made in seventeen attempts Failures were usually due to cerebral anæmia caused by clotting of blood in the anasto motic segment which occurred despite heavy heparinization of the animals

The results of a rise of pressure in the subclavian carotid segment were as might be expected reflex systemic hypotension and hypopnoea Bradycardia was not seen The absence of bradycardia was attributed without evidence to the bruising of the vagal efferent fibres in the vicinity of the subclavian-carotid angle In further experiments impulse activity was recorded from the right aortic nerve at its emergence from the angle The electroneurograms showed phasic bursts of action potentials in time with the pulse

It is interesting that Nakayama (1953*a* *b* 1954) in Japan had already shown the same responses by an almost identical technique quite unknown to the present author Nakayama s work which has only recently come to hand therefore takes precedence His experiments were performed on dogs he effected the left subclavicocarotid anasto mosis by means of a Payr cannula A rise of static pressure in the right subclavian angle

induced reflex bradycardia and a very moderate hypotension (7–18 mm Hg) Reflex effects on respiration were very doubtful Impulse activity was recorded in multi and single fibre preparation of the right superior depressor nerve The author quotes Ueda and co workers (1950) as showing that distension of the subclavian carotid segment may cause reflex apnœa Ueda and co workers (1948) are also credited with observations similar to those made by Nakayama himself

Reflexes from the Carotid Sinus

The role of the carotid sinus was not appreciated until 1923 Astley Cooper (1836) had noted that occlusion of the common carotid arteries provoked a rise of systemic blood pressure but he ascribed it to the effects of cerebral anæmia Magendie (1838) confirmed his findings and agreed with his interpretation Kussmaul & Tenner (1855) Landois (1865) Nawalichin (1870) Sewall & Steiner (1885) all repeated the experimental observation and gave the same explanation François Franck (1877) and Hedon (1910) induced bradycardia by raising the blood pressure in the perfused carotido cephalic circulation and again ascribed the response to a direct eff ct of the blood pressure on the medullary centres Porter & Pratt (1908) concurred

Tschermak (1866) announced his Vagusdruckversuch which consisted of pressing firmly on the skin of the upper part of the neck (as we now know—over the carotid sinus see Fig 41) and thus inducing cardiac slowing Tschermak (1868) thought that he was directly stimulating the motor fibres in the vagus trunk Concato (1870) stated that pressure on the carotid bifurcation seemed to be more effective than pressure over the vagus trunk but his views seemed to pass unheeded Even as late as 1925 Anrep & Starling wrote a mechanical rise in the blood pressure in the brain inhibits the vaso motor centre and stimulates the cardioinhibitory centre

Notable however among the mass of evidence collected were the contributions made by Bayliss (1893) Pagano (1900) and Siciliano (1900) Bayliss stated that occlusion of the common carotid arteries did not markedly decrease the medullary blood flow because this was largely provided by the vertebral arteries Pagano noted that the carotid bifurcation region was particularly sensitive to irritant chemical agents such as silver nitrate nicotine and sodium carbonate which caused reflex bradycardia on topical injection On the other hand he seemed to regard some degree of chemosensitivity as a property of all arteries La surface vasculaire dont l excitation peut produire par voie indirecte le ralentissement ou l arret du coeur est comprise entre l origine de la carotide commune primitive et sa bifurcation Je pourrais meme ajouter que suivant toute vraisemblance la region la plus sensible est celle la plus proche de la bifurcation carotidienne Siciliano showed that occlusion of the vertebral arteries did not cause hypertension and also showed that occlusion of the internal and external carotid arteries caused no response He wrote la pression normale exercee sur les parois des carotides communes est un des facteurs contribuant a maintenir dans leur etat tonique les nerfs inhibiteurs cardiaques

Je ne dirai que quelques mots pour eclairer l action protectrice des carotides par rapport au cerveau il est evident que la sensibilite specifique de ces vaisseaux explique mieux que toute autre hypothese l auto regularisation de la circulation cerebrale en ce sens que le mecanisme auquel elle est confiee siegeant a l entree du cerveau il n interesse

pas les elements du systeme nerveux central bien qu il les preserve contre les dangers de l anemie ou de l hyperemie

These fundamental statements of Pagano and Siciliano were unfortunately contradicted in 1912 by Kaufmann who distending the common carotid artery obtained only negative results the classical view of François Franck again prevailed Sollman & Brown (1912) came very near the discovery of the sinus reflex when they found that tugging the cephalic end of the common carotid artery even if this had been previously ligated caused bradycardia (see Fig 10) Even in 1923 however in Hering s laboratory Kisch and Sakai refuted the claims of Siciliano and Pagano stating Unsere Versuche ergeben aber weiter eine Reihe von Anhaltspunkte dafur dass die geschildert Beeinflussung der extrakardialen Herznerven bei Carotidenverschluss nicht reflektorisch durch die

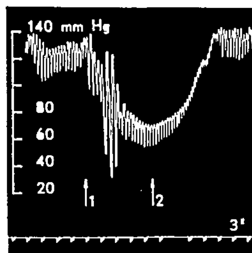


Fig 10 Systemic arterial pressure of dog The normally innervated carotid sinus is empty (ligated carotid and efferent vessels) 1–2 Longitudinal mechanical traction on cephalic end of common carotid artery—reflex bradycardia and fall of systemic blood pressure —(C Heymans De Schaepdrijver and King (1956) *Commun XX Intern Physiol Congr* p 474)

Drucksenkung in den Carotiden sondern zumindst hauptsachlich unmittelbar durch die Hypamie des Gehirns und zwar vor allem des von den Carotiden versorgten Hirngebietes bedingt wird

Mit einem Schlage aber wurde das Dunkel aufgehellt durch den wegen seiner Einfachheit und Beweiskraft klassischen Versuch von H E Hering wrote Koch (1931)

Hering came to make his discovery because of his longstanding interest in the Vagus druchversuch of Tschermak (1866 1868) In 1905 performing this test on an old lady he was struck by the fact that it was sufficient merely to press lightly with the finger on one of her carotid arteries to evoke marked cardiac slowing It seemed surprising to him that the vagus trunk could possibly be excited by such a delicate stimulus In 1919 he showed that direct mechanical stimulation of the vagal trunk did not provoke bradycardia in the dog or the rabbit on the contrary he showed that digital compression of the larynx provoked bradycardia in the rabbit (1920) he concluded that the Vagusdruckversuch might be a reflex phenomenon In 1923 he localised the origin of the reflex to nerve endings in the region of the carotid bifurcation particularly that of the carotid sinus In 1924 he proved that the excitation of the carotid sinus wall in the dog caused not only

reflex bradycardia but also reflex systemic hypotension These effects were abolished by cutting the glossopharyngeal branch which Knoll had named Sinusnerv Hering did the following experiments

1 He placed a small clip on the medial margin of the carotid sinus which caused mechanical stimulation but which did not occlude the vessel completely The heart slowed and the blood pressure fell By injecting atropine he showed that the reflex systemic hypotension still occurred although the heart rate changes no longer took place He thus demonstrated that there were two separate cardiovascular reflex responses

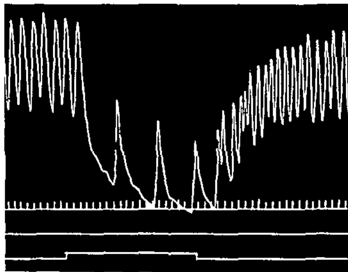


FIG 11 Heart rate and systemic blood pressure of dog Electric stimulation of right carotid sinus nerve—Reflex bradycardia and hypotension —(H E Hering (1927) *Die Karotissinus reflexe* Th Steinkopf Dresden)

2 He stimulated the central end of the sinus nerve and obtained reflex bradycardia and hypotension (Fig 11)

3 He induced the same reflex responses by tugging on the cephalic end of the common carotid artery

4 He introduced a sound into the cephalic end of the common carotid artery and stimulated the intimal wall of the sinus region upon which the same reflex responses occurred All these reflex responses were abolished by cutting the sinus nerve

5 Hering was the first to note that section of both sinus nerves caused systemic hypertension He realized that the nerve endings were tonically active in the circulation and named the nerves Blutdruckzugler

CHAPTER 4

METHODS OF STUDY OF BARORECEPTORS AND BARORECEPTOR REFLEXES

Electroneurographic Recordings of the Baroreceptor Nerves

BEFORE detailing methods of study of the sino aortic reflexes we may consider the behaviour of the baroreceptor endings themselves Many of the features of sino aortic reflex activity can be appreciated more easily from such knowledge

As stated previously Koster & Tschermak (1902) Einthoven (1908) and Adrian (1926) all reported electrical activity in the aortic nerves caused by a rise of pressure within the aortic arch and Einthoven & Adrian noted that the electrical changes occurred with each pulse However the most important study of the sinus receptors was that of Bronk

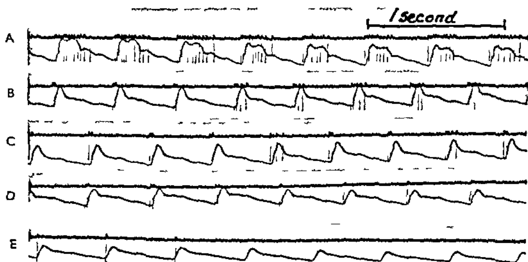


FIG 12 Figure shows impulse activity in a single fibre of the left aortic nerve and blood pressure recorded from the left common carotid artery
A Mean blood pressure 125 mm Hg D Mean blood pressure 55 mm Hg
B 80 E 42
C 62
(E Neil (1954) *Arch Middlesex Hosp* 4 16)

(1931) Bronk & Stella (1932) These workers using rabbits examined the impulse activity in the sinus nerve cut centrally recording the electroneurogram simultaneously with an optical record of the blood pressure They noted that a burst of impulses occurred with each systolic rise of the blood pressure The nerve was then thinned by dissection and in twenty five experiments a single active unit was obtained The single units fired with each systolic rise of pressure and it was noticeable that the impulse frequency was greatest

during the systolic upstroke of the pressure wave The impulse frequency tended to fall off as the blood pressure dropped from its systolic peak and in some cases the firing ceased at a point on the pressure wave at which the level of pressure was higher than that at which the impulses were being discharged during the systolic upstroke (see Fig 12) Bronk & Stella noted that when the impulses ceased during diastole at a certain pressure on lowering the mean pressure by bleeding so that the peak of systolic pressure was less than the previous diastolic pressure a systolic discharge was still usually obtained This made it clear that the mean level of blood pressure was not the sole cause of the stimulation of the baroreceptor In accordance with the behaviour of the muscle spindle as described by Adrian & Zotterman (1926) and Matthews (1931) the frequency of impulses from the mechanoreceptor of the sinus is largely determined by the rate of rise of tension or stretch which affects it These points can be clearly seen in the accompanying figure (Fig 12) which is obtained from an aortic baroreceptor at different levels of systemic blood pressure recorded via a cannula in the left subclavian artery The rapid rate of firing during the upstroke of the pulse wave and the cessation of firing during diastole before the pressure has dropped to the levels which were attended by impulse activity is shown Fig 12 (E) shows that even at a mean pressure of 42 mm Hg the rise of systolic pressure may evoke a single outburst whereas in Fig 12 (A) during diastole (mean pressure = 125 mm Hg) there is complete silence

The silence which supervenes in early diastole is not due to rapid adaptation of the receptors—on the contrary Bronk & Stella found them to be slowly adapting Again the authors compared this finding with those of Adrian & Zotterman (1926) and Bronk (1929) on the muscle spindle If the tension on a muscle be quickly reduced to a lower value the spindle frequency falls to zero or to a very low value and then slowly increases Bronk & Stella (1935) later found this to be a feature of the sinus nerve ending

Different baroreceptors were found to have different thresholds not only to steady pressures but also to the rate of rise of pressure Higher pressure in the systemic circulation caused not only increased frequency of discharge of a given unit but also caused a recruitment of additional units Thus more of the end organs became functionally active The number of impulses going to the centres in each unit of time is therefore increased as a result of higher pressure not only because of the increased frequency and duration of the discharge from the individual end organ but also in consequence of the greater number of units in action This greater number of afferent units is presumably the basis for the reflex lowering of the blood pressure

Bronk & Stella also examined the behaviour of single units at different static pressures maintained in the isolated carotid sinus Again different baroreceptors began to fire (i e had their threshold) at different pressures Any one unit however showed an increased frequency of steady firing at each increase in the static pressure until a pressure level was reached at which the impulse frequency rose no more with further increments of sinus pressure This saturation level varied with different receptors but was rarely higher than 200 mm Hg These points are illustrated by Fig 13 in which the behaviour of single units of the common carotid nerve is shown

De Castro (1951) found the sinus nerve of the cat to contain 650–700 medullated fibres Of these 3 5% were large (6–8 μ diameter) 17 5% were less than 3 μ in diameter and 79% were 3–5 μ in diameter Although these fibres belonged to group A of Erlanger

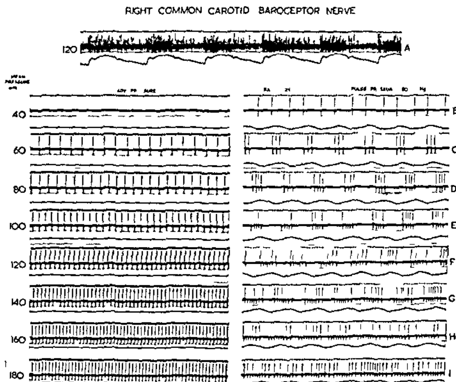


FIG 13 *Upper Record* shows the electroneurogram of a multi fibre preparation of the right common carotid baroreceptor nerve recorded simultaneously with the carotid blood pressure Note that impulse activity occurs with each pulse *Lower Record* shows the response of a single fibre of the common carotid baroreceptor nerve
On the left steady pressures rising from 40 to 180 mm Hg in the carotid segment produce an increase in the frequency of discharge of the baroreceptor unit
On the right the same baroreceptor unit is exposed to mean pressures of 40 to 180 mm of mercury but in each case a pulse pressure of 50 mm of mercury is superimposed by the use of a pump Note that the impulse discharge occurs phasically in time with the upstroke of the pulsatile pressure —(J H Green)

& Gasser s (1937) classification some are δ fibres as was suggested earlier by Zotterman (1935) in electrophysiological studies of the sinus nerve All the large fibres and some of those of medium diameter are baroreceptor—the remainder are chemoreceptor fibres according to de Castro Euler Liljestrand & Zotterman (1941) drew attention to the great number of action potentials of small size in the electroneurogram of the sinus nerve These were identified as baroreceptor potentials because of their persistence when the animal was hyperventilated with pure oxygen and because of their phasic activity in time with the pulse The Swedish workers pointed out that there were relatively few large 'spikes and argued that the small baroreceptor spikes ' were probably of much greater importance in the reflex regulation of blood pressure in view of their preponderance This view was further supported by the findings of Landgren Neil & Zotterman (1952) who found that the topical application of vaso-constrictor drugs to the sinus wall evoked a marked increase in baroreceptor impulse traffic the increase being more

particularly evident in the case of the small spikes Heymans & van den Heuvel Heymans (1950) had shown that topical application of vasoconstrictor drugs to the sinus wall caused a profound reflex fall of blood pressure

Before considering further evidence we may point out that the identification of the fibre size of a sensory neurone from the height of the action potential which can be recorded from it by laying a multiple nerve twig on saline wick electrodes is by no means a certain procedure The height of the action potential in these circumstances depends on the distance of the recording electrode from the active fibre If the multiple nerve twig contains fibres which lie between the active unit selected for study and the recording electrode then the spike height may appear quite small On cleaning the nerve twig by stripping off the unwanted fibres it is common knowledge that the spike height of the unit increases

Apart from measuring the fibre size itself which is impracticable one may infer it by making use of the relationship between conduction velocity and fibre diameter In medullated nerve fibre there is a linear relationship between diameter and conduction velocity (Gasser & Grundfest 1939 Hursh 1939 Grundfest 1940) Unfortunately the short length of the sinus nerve does not lend itself to measurements of conduction velocity We have comparable data however on the conduction velocity of baroreceptor fibres in the aortic nerve (Paintal 1953) Paintal found a range of 12–53 m /sec with a mean velocity of 33 m /sec The highest velocity is that of the largest fibres As an approximation one may say that the conduction velocity in m /sec is 5–6 times that of the fibre diameter in μ Hence 33 m /sec gives a value of about 5–6μ for the diameter and the higher velocities would correspond with the small proportion of fibres in the 6–8μ range

Landgren (1952*a*) made a detailed comparison of the behaviour of large and small baroreceptor fibres identified in terms of their spike height The reservations stated above should be considered but as Landgren was using very thin nerve preparations containing only one or two active fibres it is likely that he was genuinely recording from large and small units as he assumed

The results of his comparison revealed that there was no striking difference in the behaviour of the two types of baroreceptor in their response either to constant intrasinusal pressure or to pressure changes The adaptation curves were very similar and the impulse discharge caused by linear increases in pressure at various dp/dt values All baroreceptors showed post excitatory depression as noted by Bronk & Stella (1932) Landgren suggested that the deformation of the baroreceptor produced by stretch of the arterial wall caused a local negative membrane potential and that this depolarization fired off the impulse in the afferent fibre—similar to the changes demonstrated by Katz in the muscle spindle (1950) He considered that the post excitatory depression should be due to a dynamic off effect in which a positive membrane potential appeared which temporarily counteracted the static effect of the lower constant pressure A purely mechanical effect of the post excitatory depression cannot however be excluded e g a difference between the viscous properties of the receptor and the surrounding elastic tissue (Landgren)

Landgren showed that each receptor possessed a definite recording range of pressure within which a rise of pressure induced an increased frequency of discharge For the large baroreceptor units this extended from 30–200 mm Hg with the threshold pressure required to evoke a steady discharge varying between 80–120 mm Hg The

small baroreceptor fibres required a slightly higher threshold pressure in order to develop a steady discharge—120–150 mm Hg The large baroreceptor units exposed to the same strength of stimulus always discharged at a higher frequency than did the small baro receptors

Additional information about the behaviour of baroreceptors in the intact circulation can be found in the papers of Karasek (1933) Fischer & Lowenbach (1933) Fischer, Gantt & Lowenbach (1933) Bergami & Sachi (1935) and Rijlant (1936)

Methods of Study of the Carotid Sinus Reflexes

The discovery of the carotid sinus reflexes led naturally to an intensive study of their importance in the control of the circulation Moissejeff (1926) introduced the isolated innervated sinus preparation which greatly facilitated the experimental investigation of the reflex responses This preparation deserves a fairly detailed description The carotid *bifurcation is exposed and the external carotid and internal carotid arteries are ligated* the latter being tied on the cephalic side of the carotid sinus Both these ligatures can be placed without fear of damaging the sinus nerve The sinus nerve arises as a branch of the glossopharyngeal nerve as it lies on the tympanic bulla At its origin it is therefore on a much deeper plane than is the carotid bifurcation However the nerve then runs ventrally and laterally towards the root of the occipital artery which itself arises from the external carotid artery almost at its origin in the cat but a few mm distal to the origin of the external carotid artery in the dog Fig 1 shows the occipital artery and the ascending pharyngeal arteries in the tissue between the external and internal carotid arteries The sinus nerve runs up into this mass of tissue and ensheathing the carotid body which lies superficially near the root of the occipital artery courses on to the angle of the bifurcation where it usually runs into the medial wall of the carotid sinus It is imperative to identify the sinus nerve at its origin so that the nerve trunk can be followed up to the bifurcation Two good reasons exist for this advice (*a*) if ligatures are tied round the occipital artery and its branches without prior knowledge of the position of the sinus nerve it is likely that the nerve will be inadvertently included in one of these ligatures (*b*) many other nerve branches course in this region (see Code Dingle & Moorhouse 1936) and may be avoided in the belief that they may be the sinus nerve if the sinus nerve is identified at its origin this mistake cannot be made Theoretically in order to complete the isolation of the carotid sinus only the occipital and ascending pharyngeal arteries need now be tied If it were always possible to ligate these arteries at their origin without including any of the sinus nerve branches to the bifurcation this would be easy but this is rarely so Consequently the ligatures are placed a few mm away from the origin of these vessels and one is never certain that all arterial branches have been tied until the matter is put to the practical test Apart from such problems there are often vessel branches in this region which receiving no official name from the anatomists and only unprintable ones from the experimental physiologist will be further sources of leakage until they are secured Having tied all the ligatures which appear to be necessary the tightness of the preparation can be tested as follows the external carotid artery is held with finger and thumb of one hand to splint the sinus region and the finger and thumb of the other hand are used to expel the blood from the sinus region and the upper part of the common carotid artery

by moving the hand in the direction of the heart and finally nipping the common carotid artery in the region of the superior thyroid artery (which together with the carotid branch to the muscles has been previously tied) If the sinus is tight the segment of common carotid artery thus emptied remains slack Leakage through a patent channel causes gradual filling of the segment

After making the tight sinus the common carotid artery is ligated low in the neck and the artery is opened rostral to this There should be no bleeding after the initial loss of some of the blood contained in the segment A cannula filled with oxygenated Ringer Locke connected with a reservoir is secured in the cephalic end of the common carotid

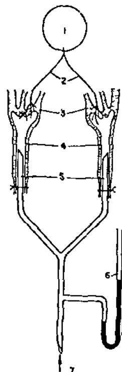


FIG 14 Method for pressure variations in isolated carotid sinus (baroreceptors) 1 Cardiovascular centres 2 Carotid sinus nerves 3 Carotid sinus 4 Balloons in carotid sinus 5 Cannula 6 Manometer 7 Tube connected with pressure device —(C Heymans A L Delaunois and G van den Heuvel Heymans (1953) *Circul Res* 1 3)

artery By adjusting the height of the reservoir the static pressure within the sinus can be varied a recording manometer can be attached to a side tube of the cannula system Moissejeff s technique is simple and remarkably effective Several disadvantages which might seem to attend its use are of little import The sinus is not perfused—but the nerve endings seem to require very little oxygen and it is not uncommon to obtain reflex responses with this preparation for several hours The temperature of the fluid within the segment is below 38°C—this reduces the activity of the nerve endings (Diamond 1955) Koch (1931) however used this preparation throughout his researches with results which are justly well known Possibly the greatest disadvantage of the Moissejeff technique is that the stimulus provided by the pressure system is non pulsatile except at the very moment of the rise of pressure As will be seen later pulsatile pressures provide a much more effective stimulus to the receptors than does static pressure and in this respect the sinus endings behave like other mechanoreceptors

Before describing the perfusion techniques proper we might mention the blind sac preparation which is very simple but quite effective for demonstration purposes The external and internal carotid and the occipital arteries are tied and the common carotid artery is tied low *in the neck A cannula carrying a balloon (made of rubber or from a* piece of jugular vein) filled with saline is slid into the common carotid artery so that the balloon tip is in the vicinity of the sinus itself (Fig 14) The saline pressure can be adjusted by varying the height of the reservoir attached to the cannula and the distension of the balloon causes deformation of the sinus (Heymans Bouckaert & Bert 1933 Cuypers 1935 Lim & Chang 1936 Donatelli & Shen 1938) This technique has the advantage that the attention to hæmostasis in the bifurcation need not be so elaborate

Perfusion of the carotid sinus bifurcation was introduced by Heymans (1929*a* *d*) with the intention of exposing the sinus endings to their natural stimulus and of providing

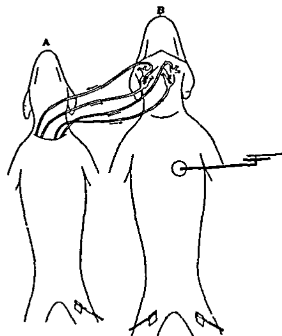


FIG 15 Perfusion of both carotid sinuses of recipient dog B by means of donor dog A Anastomoses made between common carotid arteries leading arterial blood to the sinuses Anastomoses between external carotid arteries of dog B and jugular veins of dog A returning blood to the donor dog —(C Heymans (1929) *Le Sinus carotidien)*

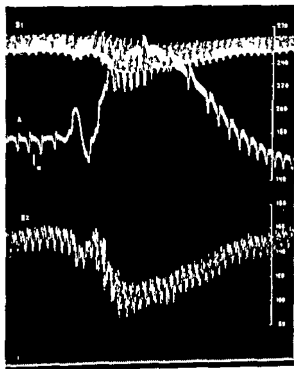


FIG 16 Records obtained by the use of the technique shown in the previous figure Records from above downwards heart rate of recipient B systemic blood pressure of donor A systemic blood pressure of recipient B and time in one second intervals At arrow a 0 1 mg adrenaline given intravenously to donor dog A Systemic hypertension occurs and hence a rise in the sinus pressure of dog B This evokes reflex systemic hypotension and bradycardia in dog B The heart rate slows from 150/minute to 90/minute —(C Heymans (1929) *Le Sinus carotidien)*

them with proper nutrition at body temperature At first a donor dog was used (A) whose common carotid artery was anastomosed by means of a Payr cannula with the cephalic end of the common carotid artery of the recipient dog (B) The efferent vessels of the carotid artery of (B) had been previously tied A Payr cannula inserted in the external carotid artery of (B) was anastomosed with the central end of the jugular vein of dog (A) (Fig 15) Peripheral resistance was provided by an adjustable clip on the efferent lead from the sinus Changes of systemic pressure induced in dog (A) thus provided the stimulus for the baroreceptor reflexes in (B) (Fig 16) Heymans & Bouckaert (1929) also used a Dale Schuster pump to perfuse the sinus and this technique has become standard The effluent fluid from the sinus is led back via a Hooker oxygenator to the reservoir of the pump Again peripheral resistance is adjusted by a screw clip The one disadvantage of the perfusion technique lie in the progressive hæmolysis which the perfused blood suffers Dogs blood is particularly prone to hæmolyse and some have preferred to use ox blood for the perfusate This naturally presupposes scrupulous ligation of all branches of the sinus We find oxygenated Ringer Locke perfectly satisfactory for perfusion The other source of trouble in perfusion arises with the necessity for a cannula in the external carotid artery It is difficult to arrange this cannula with its attached lead so that it does not drag on the bifurcation and thereby cause continuous deformation of the sinus baro receptors

M De Burgh Daly (1955) has recently used a preparation which is basically that of Moissejeff on which he has superimposed pulsations delivered by a Dale Schuster pump Other methods of investigation of the function of the sinus nerves have included (*a*) electrical stimulation of the central end of the nerve trunk (*b*) electroneurographic recording Electrical stimulation is not a very good method for the chemoreceptor afferent fibres are excited simultaneously with the true sinus afferents Only if the sinus afferents are stimulated between the carotid body and their termination is a pure baro receptor fibre effect obtained (e g Schmidt 1941)

CHAPTER 5

BARORECEPTOR REFLEXES, A STUDY OF THEIR GENERAL EFFECTS ON THE CIRCULATION AND THEIR EFFERENT PATHWAYS

A General Study of the Features of the Baroreceptor Reflex Responses

Carotid occlusion causes a rise of systemic blood pressure Even the clamping of one common carotid usually causes some rise of pressure but if both are clamped the rise is greater This as Hering showed is reflex—if the sinus nerves are cut carotid occlusion no longer evokes a rise of blood pressure (Fig 17) At the same time one can observe an important change The section of both sinus nerves causes a rise of systemic pressure As we have seen that the electrical stimulation of the central end of the sinus nerve causes a fall of blood pressure it follows that the rise of blood pressure which ensues upon sinus nerve section is due to the withdrawal of tonic inhibition exercised from these reflexogenic areas The results of Bronk & Stella (1932) furnish evidence of the tonic activity of the sinus baroreceptors Carotid occlusion however is not the ideal method of study of the reflexes as will be seen later

If one carotid sinus is isolated and perfused a rise of sinus perfusion pressure causes a fall of systemic pressure bradycardia and a diminution of breathing The systemic hypotension occurs whether or not the vagi are intact It cannot therefore be due to slowing of the heart which is largely prevented in these circumstances after vagal section It is due to inhibition of vasomotor centre discharge to the sympathetic cells governing arteriolar and venomotor tone Bronk and his colleagues (1933–34) showed that a rise of sinus pressure reduced the impulse activity in cervical and cardiac sympathetic nerves (see also Gernandt & Zotterman 1946) A characteristic feature of the reflex response of the blood pressure is that after an initial steep fall to its nadir (at the onset of the rise of sinus pressure) it tends to climb despite the maintenance of the high perfusion pressure in the sinus This is more often seen when some or all of the other baroreceptor nerves are intact If the opposite sinus nerve and the vagus nerves have been cut this secondary restoration of the blood pressure does not always occur The explanation of this lies in the tonic activity of the baroreceptors in the systemic circulation At ordinary levels of systemic pressure they discharge impulses with every pulse When the systemic blood pressure is reflexly reduced by a rise of pressure in the perfused sinus their impulse discharge is lessened or abolished and consequently the degree of tonic inhibition which they induce on the vasomotor centre is correspondingly diminished As a result venomotor and arteriolar tone undergoes a secondary improvement and the blood pressure tends to be somewhat restored The recovery is naturally very incomplete as the receptors are again stimulated as the pressure rises and therefore limit this rise

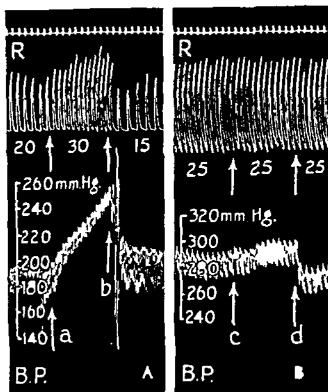


FIG 17 Reflex effects of occlusion of common carotid arteries on blood pressure heart rate and respiration (carotid sinus reflexes) Records from above downwards Time in three seconds R = respiration (inspiration = upstroke) figures below record denote rate of breathing per minute B P = arterial blood pressure

A Between a and b occlude common carotid arteries fall of pressure in carotid sinuses produces increase in rate and depth of respiration rise of arterial blood pressure and increase in heart rate At b release arteries sudden distension of carotid sinuses reflexly causes temporary inhibition of breathing slowing of heart and fall of blood pressure

Both carotid sinus nerves cut between A and B Blood pressure rises from 190 to 290 mm Hg and heart accelerates breathing increases in rate and depth

B Between c and d repeat occlusion of common carotid arteries no change in respiration or heart rate slight mechanical increase of blood pressure At d release arteries slight mechanical fall of blood pressure —(C Heymans and J J Bouckaert (1930) *J Physiol* 69 54)

Koch (1929 1931) noted that there was a threshold for the sinus reflexes This can be most easily appreciated if the other baroreceptor nerves are cut Thus if only one sinus is isolated and subjected to pressure change the contralateral sinus nerve and both vagi are sectioned Alternately both sinuses can be perfused in vagotomized animals in each case there are no opposing circulatory reflexes Raising the pressure in one sinus the other buffer nerves being cut Koch demonstrated that no reflex effects were evoked in the circulation until the sinus pressure was about 60 mm Hg (Fig 18) By raising the sinus pressure in steps (1929) and noting the change in systemic pressure he was able to plot the change in systemic pressure in response to a change in sinus pressure

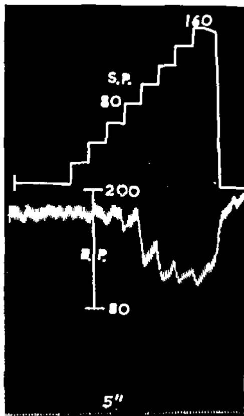


FIG 18 Dog Left sinus isolated by Moissejeff technique Right sinus nerve cut Step-like rise of static pressure in left carotid sinus Note that there is little response of the systemic blood pressure until the sinus pressure exceeds 80 mm Hg —(E Neil)

over a range of 0–240 mm Hg He obtained S shaped curves which he named Blutdruckcharakteristik curves (Fig 19) He made the important point that the sinus reflexes seemed to be maximally active at or about the normal blood pressure of the

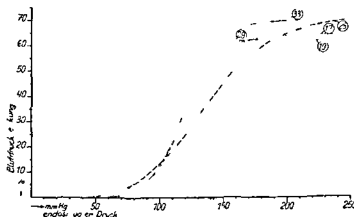


FIG 19 Blood pressure-characteristics curves of several dogs Abscissa pressure in carotid sinus Ordinate falls of systemic blood pressures —(E. Koch (1931) *Die Reflektorische Selbsteurung des Kreislaufes* Steinkopff Dresden)

animal Koch published curves of this relationship in dogs cats rabbits and monkeys In the dog (Fig 19) the maximal sensitivity of the reflex was in the region of 120 mm mercury and below 55-60 mm and above 210 mm Hg there was no response to a fall or rise of pressure respectively In the rabbit the threshold of response was 25 mm the maximum sensitivity at 95 mm Hg and there was no further response once the pressure had exceeded 160 mm Hg In the cat the comparable figures were 65 145 and 230 mm (only one experiment)

The only objection one might put forward to these findings is that they were obtained with the use of static pressures The normal stimulus to the baroreceptors is pulsatile The receptor is not as active at a steady pressure as at a pulsatile pressure with the same mean value Fig 18 shows that the rise of sinus pressure in the Moissejeff system does cause a transient response of systemic pressure as the rise occurs but when the sinus pressure becomes steady again the systemic pressure is partly restored Heymans Bouckaert & Dautrebande (1931*c*) repeated the Koch experiments using a Dale Schuster pump perfusion of the sinus They found that the maximal sensitivity of the reflex mechanisms was between 85–110 mm Hg The sensitivity of the vasomotor responses diminished progressively as the perfusion pressure rose to 200–220 mm Hg Above such values further rise of sinus pressure caused no further response Heymans Bouckaert & Dautrebande (1931) also found an abnormality of the systemic blood pressure response when the sinus pressure fell below 40–50 mm Hg Lowering of the sinus pressure from 40 mm to zero caused systemic hypotension They attributed this abnormal response to the artificial conditions of the perfusion the collapse of the sinus wall and perhaps the dragging exerted by the efferent cannula caused artificial distortion of the arterial wall which caused deformation discharge Landgren (1952) also noted that very low pressures in the sinus were sometimes the cause of impulse activity in baro receptors whose normal threshold lay at much higher values These findings are fully recognized to be due to mechanical artefacts There are no afferent endings in the sinus which are normally activated by a fall of blood pressure in the intact circulation

The threshold concept of Koch allows an explanation of the lack of reflex response to carotid occlusion when the systemic pressure is low If the systemic pressure is only 60 mm a fall of pressure in the sinus causes no change because at such a pressure the threshold of reflex response is barely reached Generally speaking the higher the level of systemic pressure the greater the response to carotid occlusion

Hering clearly recognized that the sino aortic afferent nerves acted in unison He designated them (1927 1932) Blutdruckzugler (blood pressure reins) because section of them caused systemic hypertension Kahn (1930) however preferred the term Blutdruck regler (blood pressure regulators) pointing out that the nerves served to adjust the systemic pressure to its normal value whichever way it had moved from the normal If hæmorrhage occurred the blood pressure fell and the reduction of tonic inhibition of the vasomotor centre by the baroreceptor activity resulted in increased arteriolar and venomotor constriction As a result the capacity of the system was reduced the peripheral resistance increased and the blood pressure was thus restored towards normal Samson Wright (1931 1932) translated Blutdruck regler into the now universally used buffer nerves struck perhaps by the similarity of the Blutdruck charakteristik curves to those depicting the titration curve of a buffer system Koch (1931)

preferred the term pressorezeptorische Nerven which Franklin (1937) translated presso ceptive nerves

Occasionally one sees an experimental animal in which the activity of the ' buffer nerves is very marked Fig 20 shows how such buffer activity may express itself The left carotid sinus was isolated and perfused and a rise of sinus pressure caused only a very small response of the systemic pressure The other buffer nerves were intact and successive section of them showed that the sinus reflex response had been masked by their activity One further point is to be noted Even after section of the left vagus and with the left sinus nerve subjected to minimal stimulus the systemic pressure showed little difference from that of a normal dog (Fig 20B) This can be seen to be due to the tonic activity of the right carotid sinus nerve and right vagus for when these were sectioned the blood

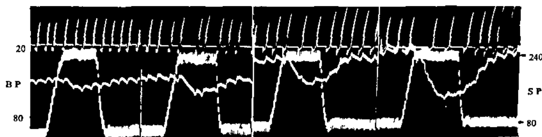


Fig 20 Dog 9 1 kg Chloralose anæsthesia Records from above downwards Respiration recorded by changes of intratracheal pressure systemic B P recorded from left femoral artery pressure in left carotid sinus isolated and perfused separately by a pump circuit

A Shows the response to rise of pressure in the left carotid sinus from 80 to 240 mm the other buffer nerves (i e both vagi and right carotid sinus nerve) being intact The fall of blood pressure is relatively slight and some recovery of pressure occurs before the sinus pressure is reduced Respiratory rate is unaffected

B After section of left vagus the systemic B P rises slightly and the respiratory rate is slower Rise of sinus pressure produces a greater fall of B P than in A

C After section of right vagus the systemic B P rises increase of sinus pressure now causes a more marked fall of systemic pressure with less recovery from the minimum level during maintenance of the raised sinus pressure

D After cutting the right sinus nerve the systemic B P again rises reaching a mean value of 2 0 mm Hg Rise of sinus pressure produces a profound fall of systemic pressure with little evidence of compensation shown Respiratory rate is markedly slowed —(E Neil (1952) *Arch Middlesex Hosp* 4 16)

pressure rose to 220 mm Hg (Fig 20D) This provides the explanation of a topic under discussion in the last century—as to whether the aortic nerves were tonically active in the intact circulation

Cyon & Ludwig (1866) Roever (1869) Pavlov (1879) and Bayliss (1893) all reported that the blood pressure was unchanged by cutting the aortic nerves Leonard Hill (1900) stated dogmatically that the nerves were not tonically active Latschenberger & Deahna (1876) however claimed that a transient rise of blood pressure occurred on cutting the nerves and Sewall & Steiner (1885) Hirsch & Stadler (1904) & Osborne (1921) agreed Osborne also reported cardiac acceleration after aortic nerve section The reason for the negative results of the earlier authors is that the sinus nerves buffer the change in blood pressure which would otherwise occur when the aortic nerves are cut

It is not clear however why the temporary and incomplete loss of baroreceptor activity caused by carotid occlusion causes such an obvious hypertension that it is used

all over the world to demonstrate the sinus reflexes to students whereas the section of both aortic nerves causes such little change in the blood pressure It is possible that part of the reflex hypertension caused by carotid occlusion is due to chemoreceptor excitation due to the reduction in blood flow through the carotid body (Euler & Liljestrand 1943 Landgren & Neil 1951)

Many regard the circulatory changes of hypertension and tachycardia produced by occlusion of the common carotid arteries as being solely due to a complete disappearance of the baroreceptor impulse activity This is not true and indeed the local conditions in the sinus region during carotid occlusion are sufficiently complicated to warrant some further description Schmidt (1932) measured the carotid sinus pressure by placing a cannula in the lingual artery and found that occlusion of the common carotid artery caused a fall of 36% of the initial pressure which gradually recovered to within 19% of its normal value This indicated that a considerable backflow of blood took place via anastomotic channels Euler & Liljestrand (1936) showed that the intrasinusal pressure resulting from occlusion of the ipselateral common carotid artery was further reduced by occlusion of the contralateral common carotid the fall being greater in cats than dogs They were the first to point out that the lowered pressure in the sinus during carotid occlusion would reduce the carotid body blood flow thereby causing chemoreceptor excitation which in turn would contribute to the reflex hypertension caused by clipping the common carotid artery

Chungcharoen Daly Neil & Schweitzer (1952) and Wang Mazzella & Heymans (1952) investigated the effects of occluding the ipselateral and contralateral common carotid or the vertebral arteries upon the pressure in the carotid sinus in the dog cat and rabbit They found that unilateral occlusion of the common carotid artery caused a fall of some 50% of the blood pressure in the carotid sinus Within 30 seconds however there ensued a rapid recovery until the pressure was within 10–35% of its initial value If the contralateral common carotid artery was occluded at the same time the fall of sinus pressure was greater By an elaborate series of experiments it was shown that the partial recovery of sinus pressure during occlusion could be attributed to blood flowing back into the sinus via the circle of Willis from the contralateral common carotid artery and from the vertebral and spinal arteries In the dog both internal carotid and internal maxillary arteries communicate with the circle of Willis The anastomotic vessel joining the orbital branch of the internal maxillary artery was found to be sometimes as large as the internal carotid artery itself (Bouckaert & Heymans 1935 Chungcharoen *et al* 1952 Wang *et al* 1952 Jewell 1952) An analogous vessel was found in the cat but not in the rabbit In the cat the internal carotid artery is not patent in its cranial segment (Davis & Storey 1943)

Action potentials recorded in the cat from a fine twig of the sinus nerve which contained chemoreceptor fibres and one baroreceptor unit showed that ipsilateral common carotid occlusion caused heavy chemoreceptor discharge only if the external carotid artery were also occluded in these circumstances there was no evidence of baroreceptor discharge whatever due to the very low pressure in the sinus region If the external carotid artery clip were then removed the intrasinus pressure rose the chemoreceptor discharge was reduced and the baroreceptor impulse activity reappeared although it was sparse in character (Fig 21)

Too much attention should not be paid to the level of mean pressure in the sinus following occlusion. Even though the mean sinus pressure may regain a level within 10–35% of its initial value in 30 seconds during occlusion the pressure is only feebly pulsatile and for this reason is much less effective in arousing baroreceptor discharge. Ead, Green & Neil (1953) showed that the reflexogenic effects of a pulsatile pressure is much greater than that of a steady sinus pressure at the same mean in so far as the systemic blood pressure response is concerned. Bronk & Stella (1932) showed that the baroreceptors responded to the rate of change of pressure by (1) increased frequency of discharge, and (2) by the recruitment of more baroreceptor units. It is for this reason that the reflex effects of common carotid occlusion are very obvious even though the mean sinus pressure may within 30 seconds regain values not far short of those initially recorded.

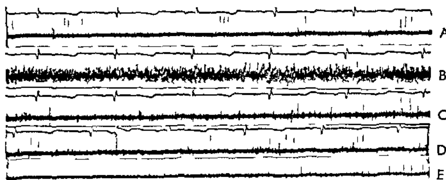


FIG. 21. Cat, 3.1 kg. Chloralose anæsthesia. Artificial respiration. Right carotid nerve cut centrally. Chemoreceptor fibres intact: all but one baroreceptor unit inactivated by dissection and crushing. Remaining buffer nerves intact. Records A, B, C and D each show e.c.g. (upper record) and action potentials from the right carotid sinus nerve (lower record). Record E shows time, 0 cycles/second and action potentials from a single pulmonary vagal stretch receptor. A, mean B.P. 130: right common carotid artery patent: right external carotid artery occluded. B, mean B.P. 135: 15 seconds after placing clip on right common carotid artery (external carotid remains occluded). C, mean B.P. 130: 10 seconds after removal of external carotid artery clip (common carotid artery remaining occluded). D, mean B.P. 125: 10 seconds after removal of the clip from the right common carotid artery.—(D. Chungcharoen, M. de B. Daly, E. Neil and A. Schweitzer (1952), *J. Physiol.* 117, 56).

Conversely, the profourd bradycardia and systemic hypotension which occur on removal of the clips from the common carotid arteries (see Fig. 17) are essentially due to the rapid rate of rise of pressure within the sinus, which powerfully excites the nerve endings.

Clearly then the effects of common carotid occlusion should not be simply interpreted as being due to complete withdrawal of sinus baroreceptor impulses. This itself is rarely so except in the few seconds following application of the clips, and in any case there is an accompanying stimulation of the chemoreceptors due to the fall of mean pressure within the bifurcation. Since the concept of the sino-aortic buffer nerves as a functional entity has arisen there has been perhaps undue enthusiasm in attempting to identify all changes in the circulation in terms of the effects produced on these afferent nerve endings. Recently however we have gained much new information about cardio-pulmonary afferent mechanisms which must be taken into account too when considering the control of the circulation. Little progress can be made until we know whether these cardio-pulmonary reflexes are tonically active or not. Meanwhile it is somewhat exasperating to find that

positive evidence of the buffer role of the sino aortic nerves is still ignored in some quarters Two examples may be given (1) It is a common mistake to claim that the baroreceptors are less active in exercise as the blood pressure rises considerably Considering that the cardiac output increases some four to six times whereas the mean pressure rises only some 50% the remarkable feature should surely be that the blood pressure rises so little Admittedly there is evidence of a great increase in the vascular bed of the muscles due to local chemical effects on the muscle blood vessels but there is no reason to suppose that the baroreceptors are any less effective during exercise (2) Boxill & Brown (1953) and Brown & Hilton (1954*a* *b* 1955) have argued in a series of publications that the rise of blood pressure caused by the intravenous injection of adrenaline or noradrenaline is not buffered by the baroreceptor reflexes They fail to understand even the basic mechanisms of the reflex An increase in blood pressure however caused must necessarily arouse greater activity in the nerve endings Unless the dose of adrenaline given is so huge that it modifies synaptic transmission then the result of the increased baroreceptor activity must be decreased vasoconstrictor discharge and hence a reflex fall in arteriolar peripheral resistance and venomotor tone which tend to offset the rise of blood pressure caused by the direct cardiovascular effects of the drug Heymans (1929*c* *d*) and Samson Wright (1930*a*) separately analysed the effects of large doses (e g 100μg) of adrenaline It is now well known that such doses cause bradycardia and apnœa these cardiac and respiratory responses were abolished by sino aortic nerve section Neither the sinus reflex response of heart rate nor that of respiration to a rise of intrasinus pressure is as easily evocable or as long lasting as that of the vasomotor centre (Winder 1937) Clearly then the baroreceptor vasomotor reflex operates even when large doses of adrenaline are given In any case Brown & Hilton seem to ignore the results of Cuypers in 1935 which entirely refute their claims Lately I H Page and co workers (1955) have confirmed the results of Heymans Wright & Cuypers They arranged one innervated sinus after the manner of Ead *et al* (1952) so that it could be alternatively supplied by the natural circulation or perfused by a pump The remaining three buffer nerves were cut state the authors (meaning both vagi and the contralateral sinus nerve) The intravenous injection of 5–10γ of noradrenaline caused an evanescent rise of blood pressure The rise was greater when the sinus was separately perfused by the pump than when it was supplied by the natural circulation

Brown & Hilton concluded from their analysis that if the baroreceptors have any biological importance it is probably more in the direction of protection against hypotension rather than hypertension This seems reminiscent of the argument referred to above that the baroreceptors are inactive in the circulation during exercise and is a complete travesty of the facts Study of their protocols reveals that in the main common carotid occlusion caused little if any rise in the systemic pressure of their animals This is very likely referable to their use of barbitone as an anæsthetic Bouckaert & Heymans (1930) showed twenty five years ago that this considerably depressed the baroreceptor reflexes Obviously if the baroreceptor reflexes are inactivated initially they are indeed unlikely to play any part in buffering changes of blood pressure however these may be caused Heymans de Schaepdryver & King (1956) have very recently performed further experiments to reinvestigate the role of the buffer nerves in limiting the hypertensive response to adrenaline They have gathered a considerable bulk of evidence which is not in harmony

with the views of Brown & Hilton The following experimental result may be selected as an example

The injection of 1 μg /kg adrenaline caused a rise in the systemic pressure of a dog from 160 mm Hg to slightly above 200 mm Hg (Fig 22 (i)) Both carotid sinus nerves and both vagi were intact The vagal and aortic nerves were cut and the blood pressure showed little change presumably due to the buffer activity of the sinus nerves The same dose of adrenaline was given again and the response differed little from the previous one (Fig 22 (ii)) Both carotid sinuses which had been previously exposed were now isolated

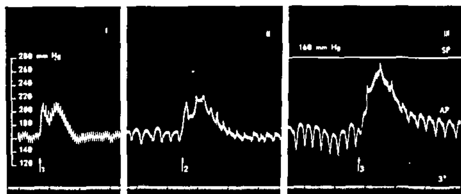


FIG 22 Dog 15 kg morphine-chloralose anæsthesia A P = arterial blood pressure S P = sinus pressure *Time in 3 second intervals*
↑ 1 Injection of 1 μg adrenaline/kg body weight Between I and II both vago-aortic nerves cut
↑ 2 Injection of 1 μg Adrenaline/kg body weight Between II and III both carotid sinuses were isolated and exposed to a steady pressure of 160 mm Hg
↑ 3 Injection of 1 μg adrenaline/kg body weight —(C Heymans A F De Schaepdryver and T O King (1956) *Arch int Pharmacodyn* 107 479)

and arranged so that the sinus pressure could be adjusted independently of the systemic circulation The pressure in the isolated sinuses was set at 160 mm Hg — the same pressure as that of the systemic circulation Injection of the same dose of adrenaline caused a much greater response than before (Fig 22 (iii)) indicating that the sinus nerves had been previously limiting the rise of pressure caused by the drug

Efferent Paths of Baroreceptor Vasomotor Reflexes

These have been mainly studied by cutting the nerves themselves or by registering *their impulse activity The important role of the splanchnic nerves in the regulation* of the blood pressure was early shown by Ludwig & Thiry (1864) and Cyon & Ludwig (1866) and was confirmed by many others e g Jansen Tams & Achelis (1924) Izquierdo & Koch (1930) Kremer & Wright (1932)

Bacq Brouha & Heymans (1934) and Schneider (1934) showed that baroreceptor vasomotor reflexes were completely abolished in dogs by complete excision of both paravertebral sympathetic chains (Figs 23 and 24) Complete sympathectomy in cats was not always successful in eliminating the baroreceptor vasomotor reflexes due probably to the speed of regeneration of the sympathetic pathways in this species (Bacq Bremer Brouha & Heymans 1939)

Parasympathetic vasodilator fibres do not participate actively in baroreceptor vasomotor reflexes (Bernthal Motley Schwind & Weeks 1945 Celander & Folkow

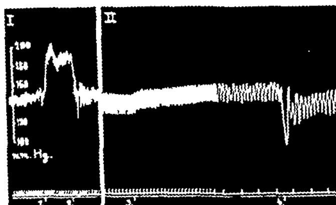


FIG 23 I Systemic arterial pressure of normal dog II Systemic arterial pressure of chronic total sympathectomized dog
1–2 Clamping and unclamping of common carotid arteries Normal reflex rise and fall of arterial pressure
3–4 Clamping and unclamping of common carotid arteries Tachycardia and brady cardia without reflex hypertension in sympathectomized dog —(Z M Bacq L Brouha and C Heymans (1934) *Arch int Pharmacodyn* 48 429)

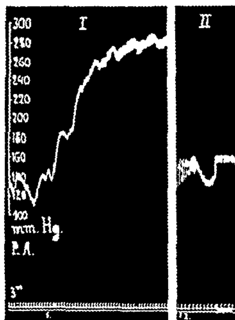


FIG 24 I Systemic arterial pressure of normal dog II Systemic arterial pressure of chronic total sympathectomized dog
1 Section of both aortic and carotid sinus nerves—hypertension
2 Section of same nerves in total sympathectomized dog—no hypertension —(Z M Bacq L Brouha and C Heymans (1934) *Arch int Pharmacodyn* 48 429)

1951 Lindgren & Uvnas 1954) It is also known that the sympathetic vasodilator nerves are not involved in baroreceptor vasomotor reflexes (Folkow & Uvnäs 1948 Lindgren & Uvnas 1954 Frumin Ngai & Wang 1953)

It follows that the efferent nervous pathway of the baroreceptor vasomotor reflex is restricted to the sympathetic vasoconstrictor nerves Central inhibition of the vasomotor centre by the baroreceptor afferents represents the only mechanism of the reflex Vaso constriction can occur in such reflexes only by a withdrawal or a reduction of the afferent baroreceptor impulses This is much more easily understood by recording the impulse activity in the sympathetic nerves themselves Gernandt Liljestrand & Zotterman (1945) showed that efferent impulses in the splanchnic nerve were greatly increased by a fall of systemic pressure produced by hæmorrhage and were conversely almost abolished by the

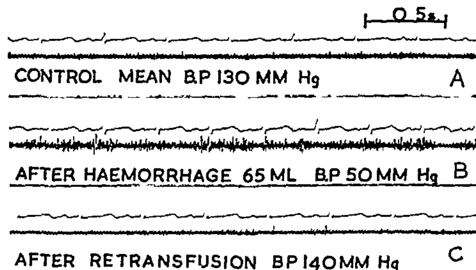


FIG 25 Cat 2 8 kg natural respiration Sympathetic ramus of right superior cervical ganglion supplying the carotid bifurcation cut peripherally and laid on electrodes Records from above downwards E C G and electroneurogram from sympathetic branch
A Control
B After removal of 65 ml blood from femoral artery
C Immediately after retransfusion
(W F Floyd and E Neil (1952) *Arch int Pharmacodyn* 91 230)

intravenous injection of adrenaline in a dose sufficient to cause marked systemic hyper tension After section of the sino aortic nerves the injection of adrenaline no longer abolished impulse activity in the splanchnic nerves proving that the effect recorded in the intact animal was reflex in origin Similarly the splanchnic efferent impulse activity was greatly increased above its resting level upon section of the sino aortic nerves Dontas (1955) has recently made some similar observations

Figure 25 shows the effect of hæmorrhage sufficient to lower the systemic blood pressure from 130 mm Hg to 50 mm Hg on the impulse activity in sympathetic post ganglionic fibres destined to supply the afferent vessels of the carotid body (Floyd & Neil 1952) The impulse activity shows a considerable increase which is partly due to the loss of reflex inhibition from the baroreceptors and partly due to reflex excitation from the chemoreceptors The replacement of the blood lost restores both the blood pressure and the sympathetic impulse activity to normal values

Chapter 6

BARORECEPTOR REFLEXES AND THE HEART

Introduction

Chaque fois qu'il constate une variation dans la hauteur du manomètre appliqué sur une artère, l'expérimentateur doit se demander quel est celui des deux facteurs de la tension artérielle qui a varié, ou bien si les deux facteurs, la puissance et la résistance, ont été modifiés à la fois. En l'absence d'un critérium qui permette de trancher en toute sûreté cette question litigieuse, bien souvent les physiologistes ont choisi l'hypothèse qui s'accordait le mieux avec leurs idées préconçues.—(Marey, 1881).

A further statement translated from Jarisch (1928) may be given—"it is a source of regret that the measurement of flow is so much more difficult than the measurement of pressure. This has led to an undue interest in the blood pressure manometer. Most organs, however, require flow rather than pressure."

These two statements are quoted here because we feel that too much attention has been paid in the past to the effects of the baroreceptor reflexes on the level of the blood pressure itself. The baroreceptors do act as "Blutdruckzügler" but their action is not confined to effects on the arteriolar resistance. Many textbooks of physiology include the following equation:

Blood pressure $=$ (or $\propto$) Cardiac output $\times$ Peripheral Resistance

This implies that provided the cardiac output remains constant an increase of peripheral resistance will increase the blood pressure. The main site of peripheral resistance is represented by the arterioles governed by the vasoconstrictor influence of the sympathetic nerves. It has become widely accepted that changes of blood pressure produced by variations of sympathetic activity are generally manifestations of changes of arteriolar peripheral resistance. It is our contention that this equation is not only of limited value but may also be actively misleading, directing attention as it does elsewhere from the capacity of the circulatory system. The capacity of the vascular bed in man is roughly 5 litres and of this perhaps 60–70% is accommodated in the post-arteriolar vessels, notably in the venules and the veins. The arteries themselves have a marked resistance to stretch as can be understood by considering the rise of pressure (40 mm Hg) produced by a systolic output of 40 ml. blood. The volume elasticity coefficient is therefore 1 mm Hg/1 ml. blood or

$$\frac{1.36 \times 981}{1} \; \frac{\text{dynes/cm}^2}{\text{cm}^3}$$

which is approximately 1 400 dynes/cm^5. The circulatory system, however, of a normal adult can accommodate a blood volume change of 1 000 ml. with a pressure change of 7 cm. water and therefore has a volume elasticity coefficient of

$$E = \frac{7 \times 981 \text{ dynes}}{1\,000 \text{ cm}^5} = 7 \text{ dynes/cm}^5$$

(Gauer Henry & Sieker (1956)) Hence the arteries can accommodate only 1/200th of any volume added to the system the remainder being accommodated in the low pressure vessels represented by the systemic veins and the intra thoracic vessels Conversely changes of capacity in the system are most likely affected by alterations of venomotor tone whether induced neurogenically or by a myogenic property of the venous walls themselves The venous system might be described as the Cinderella of circulatory physiology with good reason It has not been sufficiently understood that quite small changes produced by venoconstriction resulting in only 1 or 2% reduction of their capacity will have profound effects on the venous return to the heart Celander (1954) and Folkow (1955) have recently pointed out that as the veins contain some 60% (or more) of the total blood volume in a system in which the stroke volume of the pump is only 1–2% it can be calculated that a 1–2% reduction of venous capacity will double the diastolic inflow to the heart from one heart beat to the next A similar constriction of the arterioles would have only a negligible effect on the peripheral resistance

Much of the pre occupation of physiologists with peripheral resistance has stemmed from the difficulty of measuring changes of capacity and total flow of the vascular system The ease of measurement of the arterial blood pressure and the dramatic effects thereon which can be produced in the experimental animal by stimulation of the baroreceptor afferents have resulted in our identifying circulatory changes in terms of blood pressure and hence in terms of alterations in peripheral resistance The advent of methods of measuring cardiac output far from simplifying our understanding has in some ways fostered the cult of peripheral resistance worship It is unfortunate that when cardiac output and blood pressure are known the peripheral resistance can be calculated by simple arithmetic As a result we suffer announcements such as adrenaline is an overall vasodilator But adrenaline constricts veins (Oliver 1897—see Franklin 1937 for literature) and thereby exerts a considerable effect on the capacity of the circulation It is likely that adrenaline contributes as much to the increase of cardiac output which its administration induces by this action on venous tone as by any chronotropic and ino tropic effects which it has on the heart The result of the arithmetic however when the blood pressure is raised but the cardiac output is raised more is to show that the total peripheral resistance is reduced—which is the basis of the statement given above

Paradoxically the one instrument in frequent use in the European laboratories of the 19th century which did enable the assessment of volume changes of parts of the circulatory system gave information which was often misinterpreted The plethysmograph allows the study of changes of volume of an organ during alterations of circulatory activity From such studies it was recognized that the splanchnic organs served as blood depots—a most important concept Sympathetic stimulation was shown for example to induce splenic contraction If the innervated spleen was perfused separately however stimulation of the splenic nerves reduced the splenic volume and it was inferred that arteriolar con striction took place thereby increasing the splenic vascular resistance Unfortunately the second finding has gradually assumed greater and greater importance in the eyes of the majority and two points have been forgotten

(1) The reduction in volume of the spleen is essentially due to venoconstriction
(2) A reduction in the volume of an organ supplied by the intact circulation is no guarantee that the flow per minute through the organ has diminished Following

hæmorrhage which causes systemic hypotension there is undoubtedly a decrease in splenic blood flow for here there is increased arteriolar resistance *and* a lower perfusion pressure However in splanchnic nerve stimulation which causes marked systemic hypertension although the size of the spleen is diminished the rise of systemic pressure may well force *more* blood past the constricted arterioles because the capacity of the circulation as a whole is reduced the venous return is initially increased (by splanchnic veno constriction) and the stroke volume and cardiac output may well be increased Without measuring splenic flow in these circumstances no statement can be made from indirect evidence such as volume change

The last few years have seen a great development in methods of measuring flow and evidence collected from such studies indicates that we have been too prone to describe changes in the circulation in terms of blood pressure and arteriolar resistance Nowhere is this better exemplified than in the study of the baroreceptor reflexes where the lack of evidence of changes in cardiac output or regional blood flow has led us to identify changes of arterial pressure and organ volume solely in terms of arteriolar resistance McDowall (1935*a* 1938) has long argued that the role of the sino aortic reflexes is predominantly one of adjusting the circulatory capacity

Occlusion of the common carotid arteries causes systemic hypertension Volume plethysmographic studies of the spleen hindlimb kidney and other parts of the circulation reveal that each of these parts of the body diminishes in volume during the period of carotid occlusion Studies of the blood flow through these organs perfused separately showed that there was an increase in the peripheral resistance during carotid occlusion The systemic hypertension was therefore freely ascribed to arteriolar vasoconstriction But if all volume plethysmographic results are taken as indicating qualitative blood flow changes then we would have to conclude that the cardiac output must fall during carotid occlusion The liver spleen kidney brain and skin together receive about four fifths of the total cardiac output The flow through the brain can hardly be greater than normal at the onset of carotid occlusion and the vascular beds of all the other organs have been shown to constrict Recent direct measurements of total pulmonary flow have revealed however that carotid occlusion commonly increases the cardiac output Similarly measurements of muscle blood flow and renal blood flow indicated that the flow through these organs may increase during carotid occlusion Correspondingly then as the under standing grows that there is often an increased cardiac output during carotid occlusion so the importance attributed to changes of peripheral resistance in these circumstances declines *pari passu* There is always some increase of peripheral resistance during carotid occlusion but it is of less quantitative significance than has been considered hitherto The most important change during reflex systemic hypertension of sino aortic origin is probably that of venoconstriction Nevertheless it is true that changes of peripheral resistance caused by arteriolar constriction contribute to the high level of blood pressure during carotid occlusion In this respect peripheral arteriolar vasoconstriction is probably responsible for an increase in coronary flow which permits the heart to increase its work output In systemic hypotension caused by hæmorrhage the reflex increase in peripheral resistance in the skin and splanchnic area aids in the distribution of blood to the brain and heart circulations which are themselves relatively independent of the reflex vasoconstriction

However if vasoconstriction of the arterioles were the sole result of carotid occlusion it is arguable whether any essential benefit would be conferred on the circulation as a whole for reduction of the vis a tergo would inevitably accompany and would partially offset the effects of a rise of arterial pressure

The Baroreceptor Reflexes and Cardiac Output

There has been little agreement as to the influence of the carotid sinus reflexes on the output of the heart, this is perhaps astonishing in view of the central position that changes of cardiac output assume in any discussion of the reflex regulation of the circulation

Much of the trouble has stemmed from the use of unsuitable methods Tigerstedt (1908) used the aortic Stromuhr and noted that stimulation of the aortic nerve caused an increased cardiac output Jarisch & Ludwig (1926) Gollwitzer Meier & Schulte (1931) Moe Rennick Capo & Marshall (1949) used cardiometers Variable results were obtained and it is doubtful whether any of them can be considered to be of much significance Cardiac output in all these experiments was far below that determined in dogs with intact chest by the direct Fick method The cardiometer usually embarrasses venous return (Kenney Neil & Schweitzer 1951)

The use of the direct Fick method has itself given variable results in the hands of different workers Riml (1929) found that carotid occlusion caused either an increase or a decrease *in the cardiac output in the rabbit No doubt if his series had been larger* he would have found some animals in which the output was unchanged by this procedure Heymans *et al* (1931*c*) using the direct Fick method measured CO production and veno arterial CO difference in dogs and noted that carotid occlusion increased the cardiac output Charlier & Philippot (1947) found a rise of cardiac output in each of eight dogs subjected to carotid occlusion when using O uptake and A–V O difference for Fick measurements Kenney *et al* (1951) calculated from the protocols of Charlier & Philippot that five of the eight animals showed a fall of peripheral resistance during carotid occlusion (31 5 17 6 23 3 11 7 and 2 0% respectively) and none showed a rise of a greater degree than 4 1% In view of the marked vasoconstriction which carotid occlusion reflexly produces in the skin and splanchnic areas and in view of the mechanical obstruction of the cranial blood flow by the occlusion itself they were puzzled that there should be a decrease in the peripheral resistance

Kenney Neil & Schweitzer (1951) repeated the experiments of Charlier & Philippot and in addition studied the effects of carotid sinus perfusion pressure and carotid sinus nerve stimulation Cardiac output was determined by the direct Fick method using O uptake and A–V O difference In only one of their experiments was cardiac output reflexly decreased by a rise of sinus perfusion pressure In sixteen experiments no obvious change of cardiac output occurred De Vleeschhouwer Pannier & Delaunois (1949) obtained similar results although the cardiac index in their experiments was often very low compared with those reported by other workers (see Kenney *et al*, 1951) At about the same time Holt Rashkind Bernstein & Greisen (1946) published some results of stimulation of the sinus nerve on the cardiac output using the Stewart technique for measuring output They reported that stimulation of the sinus nerve produced an average fall of 7% in the cardiac output although the range of their results in six experiments was

quite remarkable (—23% to + 34%) Despite their own findings they calculated that 67% of the fall of blood pressure was due to a reduction of cardiac output This calculation was based on changes of cardiac output determined during the opening of an arterio venous shunt they regarded the opening of such a shunt as exemplifying a pure reduction of total peripheral resistance By substituting cardiac output and pressure changes corresponding to the alterations of T P R calculated from the results of the shunt experiments for alterations of T P R calculated from the results of sinus nerve stimulation they arrived at the conclusion stated above There is however no reason to suppose that an arterio venous shunt merely represents an alteration in T P R It is unjustifiable to analyse hæmodynamic changes occurring in one type of experiment by using results obtained in another (Kenney *et al* 1951) Leusen Demeester & de Witte (1954) using the Stewart Hamilton dye method reported that a fall of sinus pressure increased the cardiac output and that the increase of cardiac output contributed more to the rise of systemic blood pressure than did the increase in peripheral resistance calculated from their results They proceeded to examine the effect of moderate hæmorrhage on the reflex responses of cardiac output and blood pressure to changes of pressure in the isolated innervated carotid sinuses

Control measurements were first made of the effects of alterations of pressure in the perfused isolated carotid sinuses (Leusen *et al*, 1954*a b*) on the cardiac output and blood pressure of vagotomized dogs A decrease in sinus pressure caused a rise of cardiac output and blood pressure and some rise of T P R The cardiac output was increased by some 33% The T P R however increased only 20% as the blood pressure rose by some 53% The increase in cardiac output contributed to the rise of blood pressure to a greater extent than did the increase in T P R The dogs were then bled about $\frac{1}{10}$ of the blood volume being removed after which the measurements were repeated A fall of sinus pressure now increased the blood pressure by about 70% the cardiac output by about 27% and the T P R by 43% Hence as the blood reservoirs are depleted by hæmorrhage the contribution which their constriction can make during sinus hypotension becomes of less importance and the relative contribution of arteriolar vasoconstriction becomes greater (Leusen Demeester & Bouckaert 1956)

Kenney *et al* (1951) suggested that in experiments in which marked bradycardia accompanied a rise of sinus perfusion pressure there would probably be a fall in cardiac output merely due to the failure of the heart as a pump Thus if asystole supervenes as is sometimes the case when the sinus pressure is raised the heart output will obviously fall to zero In none of their experimental animals was any marked change of heart rate found possibly because they did not use morphine They conceded that sudden changes of sinus pressure might well cause transient effects on the cardiac output and discussed the inadequacy of the Fick method in detecting such changes concluding that only a beat to beat determination would suffice That of Hamilton & Remington (1947) has however been shown to be even qualitatively inaccurate by Duomarco Dillon & Wiggers (1948) The only further development of beat to beat measurements comes from some remarkable technical achievements of M de Burgh Daly & Luck (unpublished) who have succeeded in measuring total pulmonary blood flow by a rotameter during changes of isolated sinus pressure Inevitably these results were obtained in dogs with open chests under positive pressure ventilation It is unlikely that the circulatory conditions

particularly in the low pressure part of the system are the same as those extant in animals breathing normally Nevertheless it is equally unlikely that the circulatory responses obtained are *totally* dissimilar to those seen in the closed chest preparation

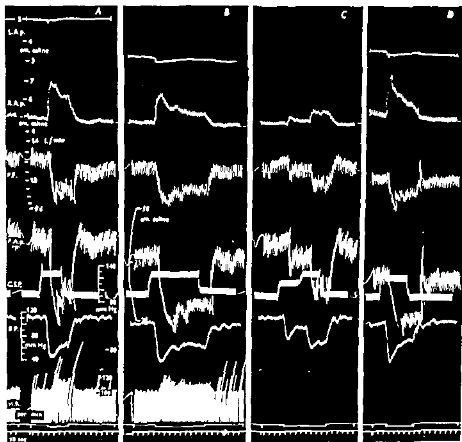


FIG 26 Dog 15 6 kg Morphine-chloralose anæsthesia Open Thorax Positive pressure artificial respiration Pulsatile perfusion of both carotid sinuses isolated from the general circulation Measurement of total pulmonary blood flow by means of a rotameter Records from above downwards left atrial pressure right atrial pressure pulmonary blood flow pulmonary arterial pressure carotid sinus perfusion pressure systemic blood pressure and heart rate

A B and *C* show the effect of raising the pressure in both carotid sinuses by different amounts and for varying periods of time In *D* the left carotid sinus only was perfused the right one now being in communication with the natural circulation Note an after rise in pulmonary arterial pressure and in pulmonary blood flow now appears —By kind permission of M de Burgh Daly

Figure 26 shows a typical result of raising the perfusion pressure in both carotid sinuses isolated from the general circulation A rise of sinus pressure from a mean pressure of 90 mm Hg to 130 mm Hg causes bradycardia a fall of systemic pressure from 110 mm Hg to 45 mm Hg a fall of pulmonary arterial pressure from about 27 cm H_2O to 20 cm a rise in right atrial pressure from 5 cm H_2O to 7 cm H_2O and a reduction in total pulmonary flow (cardiac output) from 1 25 l /min to about 0 8 l /min

In 26 tests in seven experimental animals a rise of carotid sinus pressure caused an average reduction of cardiac output of 14% (range 8–46%) The response of left and right atrial pressures was not constant—depending largely on the response of the heart they rose or fell The fall in cardiac output produced by a rise in sinus perfusion pressure was seen even in preparations in which no change of heart rate occurred in these circum stances On the other hand in animals in which marked bradycardia occurred in response to raised sinus pressure vagotomy which of course almost abolished changes of heart rate in these conditions greatly reduced the fall in cardiac output

Conversely Daly & Luck showed that carotid occlusion usually produced a rise in total pulmonary flow and in pulmonary arterial pressure

It appears from these results that the changes in pulmonary arterial pressure follow those in pulmonary flow Calculation (from the pressure drop across the pulmonary vascular bed divided by the flow) of the pulmonary vascular resistance showed that it might rise or fall during the reflex effects of raised sinus pressure The fact that the pulmonary blood flow falls in these preparations even with denervated heart and lungs points to the importance of capacity effects in the systemic circulation in promoting these changes This is probably due to reflex veno dilatation (Fleisch 1930 Gollwitzer Meier & Schulte 1931 Heymans *et al* 1931*c*) If this were the sole cause of the decreased venous return it would only be expected to be transient However the increased capacity of the venous reservoir decreases the effective blood volume and lowers the right atrial filling pressure thereby tending to maintain the diminished output of the right side of the heart A fall in right atrial pressure was observed in this type of preparation (Daly personal communication)

Be that as it may the figure included here reveals a marked rise of right atrial pressure so it is difficult to argue that the reduction of total pulmonary flow is due to other than inability of the heart itself to clear blood presented to it by the venous return There is admittedly a fairly well marked bradycardia in the preparation shown Perhaps this failure of the heart as a pump in these circumstances is the most surprising finding of all All the arguments presented in this chapter have dealt with the mechanism of venous return during the alterations of arteriolar and venomotor tone reflexly produced by variations of sympathetic vasoconstrictor activity It would seem however that the reduction of cardiac output during sinus hypertension is at least often due to a decreased efficiency of the heart itself Daly provides some important further evidence obtained from measurements of coronary sinus flow During carotid sinus hypertension there is a profound reduction of coronary sinus flow which accompanies (and is probably due to) the reflex systemic hypotension It is likely that this fall in coronary flow is responsible for the greatly diminished mechanical efficiency of the ventricle Conversely during carotid occlusion or hypotension in the perfused isolated innervated carotid sinuses a marked increase in coronary flow accompanies the reflex systemic hypertension and again probably enables the heart to maintain a greatly increased work performance represented by an increased cardiac output against a higher mean systemic blood pressure

It is fair to point out that the experimental induction of reflex hypotension in the systemic circuit by raising the perfusion pressure in the isolated innervated sinuses brings about a chain of events which is somewhat abnormal In the ordinary course of events the increased stimulation of the baroreceptors of the sino aortic region would be

caused by a rise of systemic pressure Hence the coronary flow in these circumstances would be greater than normal and it is quite possible that the marked reductions in coronary flow which Daly has recorded in his *experimental* conditions do not occur and consequently there is less chance of a fall in ventricular efficiency

The effects of carotid sinus reflexes on the cardiac output may well be determined by the state of the reservoirs in the circulation as was argued by Heymans Bouckaert & Regniers (1933)

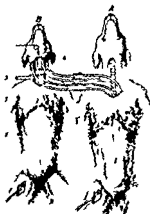
The effect of cutting the vagi on the cardiac output has been noted by Charlier & Philippot (1947) Charlier (1948) Kenney *et al* (1951) and recently by Levy *et al* (1954) Levy *et al* found no change in output and the earlier authors found no constant change As the vagi contains many fibres of baroreceptor type which arise from the cardio pulmonary area as well as from that of the aortic arch and as Aviado & Schmidt (1955) regard all baroreceptors as exerting depressant actions on the cardio vascular system this *absence of change in the cardiac output following vagotomy is surprising It suggests* that we are still rather ignorant as to the mechanisms of control Others however are much more confident Hamilton (1955) in the recent symposium on the regulation of the performance of the heart held in Atlantic City states The reflex regulation of the heart in maintaining a constant blood pressure is of course mainly a function of the reflexes originating in the stretch receptors which lie in the walls of the aortic arch and carotid sinus These reflexes slow and restrain the heart when the arterial pressure is high and cause it to speed up and increase the force of contraction when the pressure is low

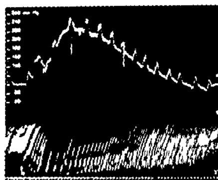
Heart Rate

Marey (1859) was the first to describe the relationship between blood pressure and heart rate Whereas he originally thought this was a direct effect of the level of the blood pressure on the heart itself he later found (Marey 1881) that after bilateral vagal section the heart rate was scarcely altered by big rises of blood pressure Bernstein (1867) and Nawrocki (1874) had already shown this Bernstein clearly stated that the blood pressure level excited the vagus centre and that the higher the blood pressure the greater was the vagal excitation The question arose as to whether the vagus centre was excited reflexly or directly Bernstein favoured the former but could not suggest the afferent pathway

François Franck (1877 1878) claimed that the level of blood pressure directly excited the vagus centre using the perfused head preparation isolated from its body save for a connection by both vagi A rise of pressure in the head circulation caused bradycardia This has been repeatedly confirmed (Eyster & Hooker 1907 1908 Lecrenier 1908 Hedon 1910 Tournade Chabrol & Marchand 1921 Foa 1921 Anrep & Starling 1925) We know now that this apparent proof is fallacious—the positive results obtained depend on whether the innervation of carotid sinuses has been preserved Siciliano (1900) and later Hering (1927) Koch & Mies (1927) and Heymans (1929) proved this (see Fig 27) Hering Koch & Heymans developed the theme that resting cardiac vagal tone is reflex and is engendered by tonic activity of the sino aortic receptors

Hering emphasized that the heart reflex induced by sinus baroreceptor stimulation was of more sudden onset than the vasomotor reflex and that its maximal effect was usually attained within a few seconds He also observed that the magnitude of the effect was much more variable than that of the vasomotor response and that it was much more





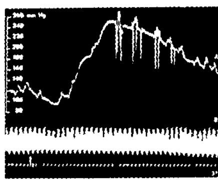


FIG 7 *Above* Method of isolated head of dog B perfused by means of dog A Vago aortic nerves alone connecting head B and body B
Left A Arterial pressure of donor dog A and head B
B Heart rate body B
1 Intravenous injection of 0 1 mg noradrenaline to dog A Rise of arterial pressure dog A and head B bradycardia in body B
Right Same preparation but carotid sinus nerves of head B are cut
1 Intravenous injection of 0 1 mg noradrenaline to dog A Rise of arterial pressure dog A and head B but no change in heart rate of body B
(C Heymans and G R De Vleeschhouwer (1950) *Arch int Pharmacodyn* 84 401)

poorly maintained Though this is generally true Fig 28 shows an exception to the rule
Schneyer (1935) also noted the poor maintenance of the heart reflex in animals with intact vago aortic nerves and concluded that this could be attributed to the influence of the aortic baroreceptors Thus as the systemic pressure fell the lessening of aortic discharge caused cardiac acceleration Spychala (1933) had reached similar conclusions and Winder (1937) also concurred Winder considered that the aortic baroreceptors were more important than were the sinus afferents in the reflex control of the heart rate he also believed that the sinus afferents were on the other hand more important than the aortic in affecting the vasomotor centre (cf Koch 1931 Izquierdo 1930 Schneyer 1935)

Danielopolu Marcu Proca & Aslan (1932) believed that sinus impulses excited both sympathetic and parasympathetic fibres together the effect of the one partially antagonizing

the other This unlikely concept dignified by the sonorous term amphotropism has disappeared from the literature of today Danielopolu and his co workers were confused by the presence of the chemoreceptor fibres in the sinus nerve which when excited cause vasomotor effects which are the opposite of those evoked by baroreceptor afferent stimulation Bronk Ferguson Margaria & Solandt (1936) made a very beautiful analysis of the effects of sinus reflexes on the impulse activity in the cardiac sympathetic nerves Cats were lightly anæsthetized and the chest wall was removed from the first to the sixth ribs respiration being maintained by a pump The long cardiac sympathetic nerves

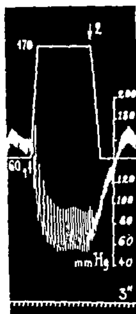


FIG 28 Dog. Rt carotid sinus isolated by Moissejeff technique A = pressure in carotid sinus B = systemic pressure (femoral artery)
1 Increase of sinus pressure induced reflex hypotension and bradycardia
2 Decrease of sinus pressure
(C Heymans (1950) Introduction to the Regulation of Blood Pressure and Heart Rate Thomas Springfield)

running from the stellate ganglia to the inferior cardiac plexus were dissected free and cut near their entrance to the plexus Placed on electrodes leading to resistance capacity coupled amplifiers and a Matthews oscillograph the nerves showed tonic impulse activity This was taken as positive evidence for the view expressed by Reid Hunt (1899) that the heart is under a continuous barrage of sympathetic impulses However the circumstances were such as would exaggerate sympathetic activity The impulses were abolished by *painting the ganglion with nicotine and were therefore postganglionic The preganglionic* pathways lay in the first five thoracic rami but mainly in the third and fourth Often the rhythm of the impulses was cardiac as had been previously shown in the hypogastric nerves supplying the blood vessels (Adrian Bronk & Phillips 1932) The cardiac rhythm was usually abolished by sino aortic nerve section Alternatively it disappeared on lowering the blood pressure Bronk (1933–4) in his Harvey Lecture includes a figure which shows the abolition of sympathetic activity which occurs when the static pressure is raised in an isolated carotid sinus

It is curious that there is no comparable evidence on the effects of carotid sinus reflexes on the impulse activity in the cardiac vagal efferent fibres

The view that the sino aortic reflexogenic zones are solely responsible for resting vagal tone is not above suspicion Certainly the heart rate usually accelerates after sinus nerve section and further quickens when the aortic nerves themselves are cut The oft repeated statement that subsequent vagal section causes no further acceleration is not invariably true It would be remarkable if it were so when one considers that numerous cavo atrial and ventricular vagal receptors have been found to be tonically active Their afferent fibres show bursts of impulses with a cardiac rhythm The stimulation of these cardiac afferents may cause profound bradycardia and has never been known to evoke cardiac acceleration (Jarisch & Zotterman 1948) Aviado & Schmidt (1955) consider that all baroreceptors from the cardio pulmonary area cause reflex bradycardia If this is so then it is extremely puzzling how the heart rate so commonly escapes early in the response induced by a rise of sinus pressure As the heart slows initially we have seen that there is often a marked rise of right atrial pressure One might expect this to cause stimulation of the atrio caval receptors and as a result to induce a further slowing of the heart The reverse is the case—the heart rate quickens towards its normal value Indeed it occasionally speeds beyond its ordinary rate (Schneyer 1935 Winder 1937) This may represent a direct effect of increased tension on the muscle fibres (due to the greater filling) causing acceleration of the beat (as noted by Ludwig & Luchsinger (1881) and Hobbs Hyder & McDowall (1926) in the frog heart and Tiitso & Tootson (1935) and Blinks (1956) in the mammalian heart) Alternatively it may be a break through of a cardio acceleratory reflex which contrary to the beliefs of Aviado & Schmidt (1955) arises from baroreceptors in the cardiopulmonary area

There is still disagreement as to whether the sino aortic nerves exert only a unilateral influence on the cardiac vagal centre Roever (1869) found that stimulation of the aortic nerve in the rabbit induced bradycardia only if the homolateral vagus was intact Heymans (1929) agreed as did Scott & Reed (1955) and Kazem Beck (1888) Izquierdo (1930) and Wang & Borison (1947*a* *b*) on the other hand claim that there are limited contralateral vagal motor effects

The most careful study of the extra vagal component of the sinus baroreceptor heart rate reflex is that of Winder (1938) in which he studied the response of the heart rate to a rise of pressure in the perfused carotid sinuses maintaining constant arterial pressure and ventilation The dogs were vagotomized and the cervical sympathetic trunks were cut The maximal cardiac slowing obtained by raising the sinus pressure was 8 / The relationship between heart rate response and sinus pressure was sigmoid The brady cardia which was thus induced must have been due to reflex inhibition of the cardiac sympathetic nerves as noted previously by Hering (1927) Tournade (1930) Bronk *et al* (1936) Govaerts (1936) and Rijlant (1936)

CHAPTER 7

BARORECEPTOR VASOMOTOR REFLEXES

Abdominal and Thoracic Circulation

Kidney

THERE is a huge amount of evidence largely derived from volume plethysmography which supports a belief in baroreceptor reflex vasomotor effects on the renal circulation Thus Cyon & Ludwig (1866) Roever (1869) Bradford (1889) Bayliss (1893) Hallion & François Franck (1896) showed that stimulation of the aortic nerve caused an increase in the kidney volume due to vasodilatation

Sollman & Pilcher (1912) and Sollman & Brown (1912) observed renal vasodilatation in the perfused innervated kidney on stimulation of the aortic nerve and on traction of the common carotid respectively Heymans (1929*d*) showed that common carotid occlusion evoked reflex vasoconstriction of the innervated kidney separately perfused by a donor dog

None of these experiments indicates however what changes of blood flow occur through the renal circulation in the circumstances of systemic hypertension produced by carotid occlusion The results obtained by Heymans (1929*d*) and Sollmann and his colleagues prove that changes of calibre of the renal vessels occur as a result of sinus and aortic reflexes They do not however indicate what the overall effect is when the raised systemic pressure opposes the local vasoconstriction Obviously volume plethysmography indicates only a change in volume of the organ and can give no information of the blood flow through it *As it is usually accepted that about two thirds of the circulating* blood volume is in the venous side of the circulation at any one time it is reasonable to believe that this is true of the renal circulation itself Hence venoconstriction which is now an established fact in reflex circulatory responses to carotid occlusion may itself be largely responsible for the diminution in renal volume without there necessarily being a marked renal arteriolar constriction Even if arteriolar vasoconstriction be admitted to be considerable we must take into account the marked rise in systemic pressure which will itself tend to increase renal flow The final result of these two conflicting factors can be studied only by the measurements of renal blood flow itself Kenney & Neil (unpublished) obtained some evidence on this in experiments in which glomerular filtration rate and renal blood flow were measured in dogs in which saline diuresis was induced as a back ground and both carotid sinuses were isolated and perfused G F R and R P F were measured respectively by inulin (or sodium thiosulphate) and P A H clearance This *technique possesses the obvious advantage that the local renal innervation is undisturbed* Homer Smith (1951) has brilliantly summarized the criticisms which may be made of any technique of study of the renal circulation which involves laparotomy and the forcible manipulation of the kidney required for the insertion of a thermostromuhr or for the application of an oncometer Even the classical observation of Claude Bernard (1859) that section of the splanchnic nerve caused an increased flow of urine on the operated side

(from which he somewhat rashly concluded that increased renal blood flow had occurred) cannot be substantiated if the same procedure in so far as it affects the kidney circulation be carried out on the unanæsthetized untraumatized animal Thus Rhoads and co workers (1934) found that local anæsthesia of the explanted kidney did not modify renal blood flow It would seem probable therefore from this and other evidence cited by Smith (1951) that renal vasoconstrictor tone is excessive in laparotomized animals and that the reflex responses of sino aortic stimulation studied in this manner may be misleading

Kenney & Neil indeed found that the renal blood flow was normally increased by carotid occlusion and was occasionally unchanged Obviously then the increased systemic pressure may overcome the local increase in arteriolar peripheral resistance but is occasionally offset by it Conversely a rise of perfusion pressure in the isolated carotid bifurcations usually evoked some reduction in renal blood flow and never caused increased blood flow through the kidney As far as their results go they indicate that the local renal innervation may be protective in preventing excessive changes of renal blood flow despite marked changes of systemic pressure This is not out of keeping with the views of Smith although he concludes that the renal circulation can adjust itself to changing arterial pressure to maintain constancy of flow even when the kidney is denervated

Since the time of Claude Bernard (1859) the mistake of identifying changes of urine flow consequent to alterations of sympathetic activity as being due to changes of blood flow has been made repeatedly Thus Malmejac (1934) claimed that carotid occlusion caused reflex oliguria whereas a rise of sinus perfusion pressure produced diuresis and simply assumed that these alterations of urinary volume were due to reflex changes of blood flow Apart from the illogicality of such an argument the experimental findings are themselves questionable Carotid occlusion commonly causes diuresis in the anæsthetized dog (Kenney & Neil) and invariably increases the urinary volume in the unanæsthetized dog (O Connor 1955) After denervation of the kidney the same occurs and is therefore referable to the increase in systemic pressure Kenney & Neil usually found a diminution in urine flow accompanied the reflex systemic hypotension produced by raising the carotid sinus perfusion pressure

Spleen

Heymans (1929*c*) and Heymans *et al* (1931*c*) showed that alterations of carotid sinus perfusion pressure caused reflex changes of calibre of the splenic vessels A donor dog (A) was used to perfuse the carotid sinus of a dog (B) whose innervated spleen was in turn perfused by a second donor dog (C) (Fig 29) Driver & Vogt (1950) found that carotid occlusion evoked reflex splenic contraction in cats the effects being mediated via the splenic sympathetic nerves Holtz & Schumann (1949) obtained similar results Again however there is no evidence as to the changes of splenic *blood flow* which occur when the spleen is supplied by its own natural circulation

Mesenteric Blood Vessels

Bayliss (1893) Bunch (1899) and Jarisch & Ludwig (1926) showed that an intestinal loop enclosed in an oncometer increased in volume during stimulation of the aortic nerve Tournade (1930) found stimulation of the sinus nerve to be equally effective and conversely Koch & Nordmann (1928) demonstrated that mesenteric vasoconstriction ensued upon

carotid occlusion Heymans Bouckaert & Dautrebande (1931*c*) demonstrated mesenteric vasoconstriction as a reflex response of raised perfusion pressure in the isolated carotid sinus and drew attention to the important role which mesenteric blood vessels may be considered to play as blood depots in the reflex regulation of the capacity of the circulatory system

Liver

Heymans *et al* (1930 1931*c*) and Gollwitzer Meier & Schulte (1931) showed that the volume of the liver can be modified by reflexes originating from the carotid sinus A rise

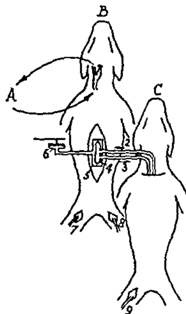


FIG 29 Diagram to illustrate carotid sinus reflexes on spleen volume
A = donor dog A perfuses the isolated but innervated carotid sinus of dog B B = dog B C = dog C perfuses the isolated innervated spleen of dog B
2 Carotid artery of dog C anastomosed with splenic artery of dog B
3 Jugular vein of dog C connected with splenic vein of dog B
4 Spleen of dog B is enclosed in an oncometer connected with a tambour (6)
7–8 Heart rate and blood pressure of dog B are recorded
9 Heart rate and blood pressure of dog C
(C Heymans (1950) Introduction to the Regulation of Blood Pressure and Heart Rate C Thomas Illinois)

of sinus perfusion pressure induced an increase in hepatic volume and conversely carotid occlusion provoked a decrease in liver volume They considered that the liver was an important blood depot whose size could be modified by sino aortic reflexes thereby making available blood for the supply of the heart and brain in the circumstances following hæmorrhage

Lungs

Relatively few studies have been made on the effects of sino aortic reflexes on pulmonary hæmodynamics Many of the early workers Lichtheim (1876) Bradford & Dean (1889 1894) Wood (1902) Weber (1911) stimulated the central end of the vagus and evoked a rise in pulmonary arterial pressure but it would be unreasonable to suppose that such a response was induced by afferent impulses in the aortic nerves only Schafer (1920) however stimulated the aortic nerve itself in the vagotomized rabbit and found a fall in arterial pressure A similar result was obtained by sinus nerve stimulation in the vagotomized dog by Tournade & Malmejac (1932) and Burstein (1946) Others however

have claimed that carotid sinus stimulation caused no effect on the pulmonary arterial pressure (Miguel Mora & Vina 1946 Euler & Liljestrand 1946 Condorelli 1952)

Conversely carotid occlusion or a fall in carotid sinus perfusion pressure has been claimed by some to cause a rise in pulmonary arterial pressure (Burstein 1946 Leusen Demeester & Bouckaert 1954) and by others to cause no change of pulmonary arterial pressure (Aviado *et al* 1952)

Schafer (1920) made no measurements of left or right atrial pressure yet argued that the fall in pulmonary arterial pressure on aortic nerve stimulation was the result of two opposing factors—increased venous return to the right heart which was outweighed by pulmonary vasodilatation

De Burgh Daly & Schweitzer (1956) have recently added greatly to our understanding of the problems involved in a large series of carefully controlled experiments in dogs with open chests Bilateral occlusion of the common carotid arteries or section of one carotid sinus nerve caused reflex systemic and pulmonary hypertension In both cases the pulmonary hypertension gradually subsided A rise in perfusion pressure in the isolated carotid sinus caused systemic and pulmonary hypotension and bradycardia The percentage changes of pulmonary arterial pressure caused by these procedures was smaller than those occurring in the systemic pressure due probably to the greater dis tensibility of the pulmonary vascular bed In experiments in which the heart and lungs were denervated carotid sinus reflexes still induced changes of pulmonary arterial pressure qualitatively similar to those evoked in animals whose cardio pulmonary innervation was intact In these denervated preparations pulmonary arterial pressure changes were accompanied by similar directional changes in pulmonary blood flow (Daly & Luck) which were in turn related to capacity effects in the systemic circulation due to alterations of venomotor tone Daly & Luck (unpublished) have shown that sinus baroreceptor stimulation causes an almost invariable decrease in total pulmonary flow Hence there is no reason to *assume* that the fall in pulmonary arterial pressure necessarily represents any alteration of pulmonary vascular resistance at all

The Coronary Vessels

As the coronary arteries are abundantly innervated it might be expected that sino aortic reflexes would play an important part in modifying the coronary flow Unfortun ately the stimulation of the heart nerves affects also the activity of the myocardium and the net effect of this mixed stimulation is a vasodilatation (Gregg 1950) As Folkow (1955) has said to draw a parallel it would not be easy to evaluate the effect of the constrictor fibres to the skeletal muscles if their motor nerves were always stimulated concomitantly

The innervation of the coronaries has been studied particularly by Woollard (1926) Nettleship (1936) and Nonidez (1939) Woollard found that the innervation was by both vagal and sympathetic branches Large myelinated fibre endings in the adventitia were vagal sensory Sympathetic fibres tended to end in the media and such endings were found as far as the arterioles Bilateral stellate ganglionectomy caused disappearance of the majority of the endings in the media of the large branches but less change in the media of the smaller coronary vessels He concluded that the surviving nerve fibres supplying the small vessels were parasympathetic Nettleship confirmed and extended

his results Nettleship also found that most of the afferent nerves from the coronaries ran to the lower thoracic dorsal roots Thus these fibres survived stellatectomy and vagotomy but degenerated after ablation of the lower thoracic spinal ganglia

Acetylcholine dilates the coronaries in all concentrations (Folkow 1955) It is probable that all sympathetic vasodilators are cholinergic (Uvnas 1954) so if the coronaries receive in addition to a vagal supply such an innervation as it is claimed (Gregg & Shipley 1944) this might offset the effect of a sympathetic constrictor innervation In any case the effects of the innervation may be overshadowed by the local action of metabolites—notably those produced during oxygen lack (Hilton & Eichholtz 1925) Stella (1931) examined the effect of sinus reflexes on the coronary outflow measured by collecting blood from the coronary sinus by means of a Morawitz cannula He used a heart lung head preparation in which the left sinus was denervated and the right carotid sinus was isolated and perfused An increase in sinus pressure caused the usual bradycardia which was accompanied by a fall in cardiac output and a great reduction in coronary flow (*vide* Daly & Luck in cardiac output section) By driving the heart electrically he was able to prevent the fall in rate and output whereupon sinus hypertension evoked a fall in coronary outflow which was much less conspicuous than before Similar results had been obtained by Anrep & Segall (1926) It is difficult to explain Stella s results without postulating that the coronary vessels are tonically subjected to the effects of a sympathetic vasodilator discharge Noradrenaline dilates and adrenaline constricts the coronaries according to D J Smith (in a personal communication cited by von Euler (1956)) The subject is a confused one Although as we have seen sinus stimulation causes a profound fall of coronary flow which may contribute to the loss of ventricular efficiency which Daly & Luck recorded in the intact circulation one would never see sinus stimulation occurring together with a marked fall of mean systemic pressure The coronary flow depends mainly on mean pressure and on local chemical factors and we consider that the sino aortic reflexes exert a relatively unimportant effect on this circulation

The Cephalic and Cerebral Circulation

It is generally admitted that the cerebral circulation is not greatly influenced by changes in vasomotor activity (see Bouckaert & Jourdan 1949 Schmidt 1950) Those who favour this type of argument stress the advantage thereby enjoyed by the cerebral circulation Alterations of vasomotor activity which induce changes of arteriolar resistance and venous capacity elsewhere in the vascular system thereby secure for the brain a satisfactory level of mean systemic pressure which determines its blood flow if the cerebral vessels were themselves affected to any great degree by vasomotor changes then the resultant altera tions of cerebral vacular resistance would offset the effects of the changes of systemic pressure produced by sympathetic activity elsewhere in the general circulation

It is true that a sparse innervation by the sympathetic fibres exists moreover functional studies have revealed that the vessels of the hypothalamus (Schmidt) and the parietal cortex (Schmidt & Hendrix 1938) may be subjected to sympathetic vaso constriction However the medullary vessels and those of the pons and occipital cortex are insensitive to sympathetic stimulation Dumke & Schmidt (1943) were unable to record any reduction of total cerebral blood flow measured in monkeys with the bubble flow meter during strong sympathetic stimulation Heymans & Bouckaert (1929 1932)

have shown correspondingly that the cerebral blood vessels do not participate actively in the baroreceptor reflexes

The tone of the extra cranial vessels on the other hand is considerably modified in the appropriate way by changes of sinus pressure (Heymans & Bouckaert 1928 1930 Schmidt & Hendrix 1938) Rein (1929 1931) showed that reflex vasoconstriction of the extracranial circulation particularly affecting the external carotid artery and its branches shifts the blood from the extracranial to the intracranial vessels Concato (1870) Holtmeier (1927) Gaisbock (1928) and Koch & Simon (1928) noted reflex vasodilation of vessels of the face occurred during mechanical stimulation of the carotid sinus area in man The extracranial vessels essentially act as shunts or reservoirs for the cerebral circulation and serve to protect the brain against variations in blood pressure thereby helping to regulate and steady the cerebral blood flow

Rein (1931) has claimed that the thyroid also acts as a shunt for the cerebral circulation for reflex vasodilatation of the thyroid vessels occurs during sinus hypertension and conversely a fall of sinus pressure evokes reflex constriction of the thyroid vasculature However as the thyroid weighs only 30 g even with its high rate of flow 500 ml /100 g /min it can only contribute in a minor extent to this end

The brain conducts itself as an organ in a state of high metabolic need Its blood supply depends essentially upon the mean blood pressure and on local chemical factors The constancy of cerebral blood flow depends primarily on the constancy of the blood pressure The sino aortic receptors are largely responsible for the regulation of blood pressure and cardiac output but effect this regulation by mechanisms which operate in the remainder of the vascular system and which have little if any effect on the cerebral blood vessels themselves

Peripheral Circulation

Limbs

Porter & Pratt (1908) found that the vessels of an isolated but innervated perfused limb constricted when the systemic blood pressure fell and conversely that they dilated during a period of systemic hypotension Their results were confirmed by Tournade Chabrol & Marchand (1921) Each group of workers believed these vasomotor effects to be due to an action of the systemic blood pressure on the centres themselves Sollmann & Brown (1912) claimed that traction on the cephalic end of the common carotid artery induced a decrease in limb volume Rein (1931) found a decrease in femoral blood flow as measured by the thermostromuhr when the common carotid arteries were occluded despite the fact that marked systemic hypertension occurred simultaneously He concluded that the reduction in baroreceptor activity induced a profound reflex vaso constriction Heymans Bouckaert & Dautrebande (1931*c*) perfused the innervated isolated limb and proved that a rise of sinus pressure induced reflex vasodilatation and conversely that a fall of sinus pressure caused vasoconstriction Grimson & Shen (1939) repeated these studies on the skinned limb and obtained similar results which indicated that the muscle blood vessels themselves were subjected to reflex variations in sympathetic vasoconstrictor tone induced by alterations of systemic pressure which affected the baroreceptors (see Jarisch 1925) McDowall (1950) however claimed that the sympathetic constrictor tone of the muscle blood vessels was relatively insensitive to sinus reflexes in

the cat Many of his experiments were done with volume plethysmography which affords no direct evidence but he states on p 7 of his paper that the vascular resistance of a perfused skinned hind limb was indeed increased by carotid occlusion Lindgren & Uvnas (1953 1954) have more recently provided convincing evidence that the sympathetic vaso constrictor tone of the muscle blood vessels *is undoubtedly modified by baroreceptor* reflexes Thus in a perfused skinned hind limb electrical stimulation of the sinus nerve caused marked vasodilatation Although the sinus nerve contains both chemo and baro receptor fibres, these results were reasonably ascribed to a preponderant reflex effect exerted by the baroreceptor fibre stimulation Although the muscle vessels receive a cholinergic sympathetic vasodilator innervation (Barcroft *et al* 1944) it has been shown that these fibres are entirely unresponsive to baroreceptor reflexes (Folkow & Uvnas 1948) being activated only by corticohypothalamic excitation (Eliasson *et al* 1951 Lindgren & Uvnas 1953 Uvnas 1954) Thus baroreceptor reflexes may be abolished by cauterization of the medullary depressor area which nevertheless fails to affect the sympathetic vasodilatation induced by hypothalamic stimulation Hence it follows that the vasodilator effects in muscle vessels induced by baroreceptor reflexes are effected only by reflex inhibition of sympathetic vasoconstrictor tone (Frumin Ngai & Wang 1953) In keeping with this conclusion atropinization which entirely abolishes the effect of sympathetic vasodilator fibres does not modify the vasodilatation induced in the muscle by sinus nerve stimulation *ergotamine in sympatholytic doses does* however abolish this reflex response

In Lindgren & Uvnas s experiments (1953 1954) stimulation of the sinus nerve caused a diminution in blood flow through the intact leg due to the profound fall in systemic arterial pressure which masked the vasodilatation demonstrable when the limb was perfused separately at constant pressure This result reveals how misleading flow measurements can be unless attention is paid to maintaining a constant blood pressure Nevertheless they do reveal the actual state of affairs in the intact circulation in which the overall increase of systemic venous capacity caused by the baroreceptor reflex offsets the vasodilatation in the muscle vessels and causes a reduced venous return from the muscles Daly & Neil (unpublished) using a rotameter measured the blood flow through the skinned hind limb of a dog during changes of pressure in the isolated innervated carotid sinus Despite marked falls of systemic blood pressure produced by a raised sinus pressure the muscle blood flow increased It is clear therefore that the baroreceptor reflexes cause muscle vasodilatation which may be sufficiently great to offset the fall of systemic blood pressure and which may therefore allow a greater muscle blood flow (see Folkow 1952 and Celander & Folkow 1953)

Secretion of the Adrenal Medulla

Tournade & Chabrol (1926) showed that arterial hypotension stimulated adrenaline secretion and conversely that a rise of systemic pressure inhibited this secretion They had at first attributed these changes to a direct action of the blood pressure on the centres regulating adrenal medullary secretion They based this opinion on their demonstration that sudden ischæmia of the brain produced by ligation of the vertebral arteries and temporary occlusion of the common carotid arteries induced marked adrenaline secretion They strongly supported the view that there was a resting secretion of adrenaline in

normal physiological circumstances Heymans (1929*a* *b*) made use of the ingenious suprarenal jugular venous anastomosis of Tournade & Chabrol (1926) The sinus of a recipient dog (B) was perfused by a donor dog (A) The right suprarenal vein of (B) was anastomosed by means of Payr cannulæ via a length of jugular vein with the jugular vein of a third dog (C) (Fig 30) The volume of the spleen of (C) measured oncometrically reflected alterations of adrenaline secretion in dog (B) produced by changes of sinus pressure The left suprarenal gland was extirpated A fall of sinus pressure in dog (B)

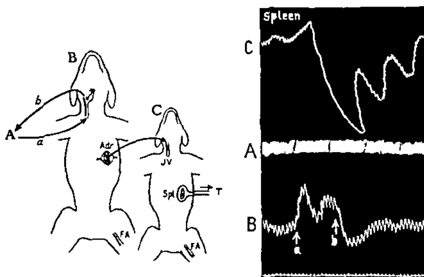


FIG 30 *Left* Diagram to illustrate carotid sinus perfusion and suprarenal jugular anastomosis A = dog A perfusing by carotid (a) and jugular (b) anastomosis the circulatorily isolated but innervated carotid sinus of dog B Adr = anastomosis between the suprarenal vein of dog B and the jugular vein (J V) of adrenalectomized dog C Spl = volume changes of the spleen due to the catechol secretions of dog B are recorded by means of an oncometer connected to a tambour T *Right* Shows records obtained by this technique Records from abo e down wards C = volume of spleen A = blood pressure of dog A B = blood pressure of dog B At *a* sinus hypotension in dog B was induced by occluding the carotid artery used for perfusion A rise of systemic pressure in dog B was accompanied by a fall in the splenic volume of dog C caused by the reflex secretion of adrenaline by dog B On releasing the sinus perfusion the splenic volume returned to its previous value —(from C Heymans (1929) *C R Soc Biol* 100 199)

caused adrenal medullary secretion which produced splenic contraction in dog (C) A rise of sinus pressure caused a reflex dilatation of the splenic vessels It seems almost certain therefore that the results attributed by Tournade & Chabrol to the direct effects of blood pressure on the medullary centres are essentially reflex in nature These classical experiments cannot of course be cited in proof of a resting secretion of adrenaline in the normal intact animal the extensive nature of the operative procedure must have favoured excessive sympathetic discharge

Sino aortic effects on adrenaline secretion by the adrenal medulla have been generally confirmed von Euler & Liljestrand (1934) found that the adrenaline level was raised during carotid occlusion although they detected no rise in the blood sugar level Aomura (1930) obtained an increased adrenaline secretion on clamping the carotid arteries and

conversely obtained a drop in this secretion when stimulating the carotid sinus Hartwich & Hessel (1931) reported similar results Holtz & Schumann (1949) found that clamping the carotids caused a rise in blood pressure and splenic contraction but caused no change in the blood sugar level and did not induce intestinal inhibition On administering adrenaline in doses just sufficient to produce the same splenic contraction as was evoked by carotid occlusion they obtained inhibition of intestinal movements The administration of noradrenaline in similar doses did not cause intestinal inhibition Clamping the carotids in adrenalectomized animals did not induce splenic contraction and they concluded that the contraction of the spleen was due to a reflex liberation of noradrenaline by the suprarenal glands Driver & Vogt (1950) obtained splenic contraction during carotid occlusion in cats under sodium pentobarbitone anæsthesia but found that this contraction was abolished by section of the splenic nerves and that it was unaffected by adrenalectomy Carotid occlusion did not produce a shift in the ratio of adrenaline/noradrenaline in the adrenal venous plasma and Driver & Vogt were unable to detect any increase in the output of adrenaline like substances by the adrenal medulla These results may be related to the depressant effect of sodium pentobarbitone on the sino aortic reflexes the blood pressure response to carotid occlusion which they list in one animal was very feeble They note incidentally that occasionally the vagi were cut in the neck This however did not greatly enhance the size of the blood pressure response to carotid occlusion This is unusual On the other hand their very finding of splenic contraction indicates that sinus reflexes were present Brauner Brucke & Kaindl (1950) reported that on repeated carotid occlusions there was increased outpouring of catechols of which the larger proportion appeared to be adrenaline Brauner Brucke Kaindl & Neumayr (1950) also found an increased secretion of catechols but could detect no preponderance of noradrenaline secretion Kaindl & von Euler (1951) showed that carotid occlusion increased the rate of secretion of adrenal catechols up to four times but could detect no alteration in the proportions of the two catechols compared with that secreted under resting conditions Kaindl & Euler stated that no increase in the secretion rate occurred unless both vagi were cut As von Euler (1956) notes it is interesting that the composition of the secretion (60–89% noradrenaline) differs so considerably from that of the content of the gland which on an average is 45% noradrenaline Eranko (1956) has recently shown that treatment of the adrenal with formalin causes fluorescence in certain cells of fresh frozen adrenal sections The non fluorescing cells contain a large amount of adrenaline but little noradrenaline while the fluorescing cells contain noradrenaline von Euler who has done much to show that noradrenaline is the chief adrenergic nerve *mediator in mammals (1946 1948 1950 1951) has suggested that the main function of noradrenaline* seems to be the normal control of the circulation Adrenaline on the other hand produces marked effects on oxygen consumption and the blood sugar level (besides its well known cardiovascular actions) which are of value in conditions of stress In keeping with this suggestion the stimulation of afferent nerves (sciatic or brachial plexus) causes a marked outpouring of adrenaline by the suprarenal medulla but induces no secretion of noradrenaline Folkow & Euler (1954) confirmed previous findings of Brucke Kaindl & Mayer (1952) that electrical stimulation of the hypothalamus induced a considerable increase in the suprarenal secretion of adrenaline This effect was obtained by stimulations of the upper part of the posterior paraventricular area Adjacent parts of the

hypothalamus caused the opposite response when stimulated—a larger amount of noradrenaline was secreted by the suprarenals

In view of these suggestions it is not surprising that the withdrawal of sinus baro receptor inhibition from the vasomotor centre should cause an increased suprarenal secretion which may contain up to 90% noradrenaline However it is now clear that the secretory activity of the adrenals plays only an accessory role in the sino aortic reflexes Nowak (1938) has shown that the baroreceptor vasomotor reflexes occur normally in adrenalectomized animals maintained by cortical extracts (see also Heymans & Bouckaert 1934) Celander (1954) has found that the blood vessels are completely dominated by their vasoconstrictor fibres and claims that the effects of catechols naturally secreted by the suprarenal medulla were negligible In this respect the results of Van Loo Surtshin & Katz (1948) are worth mentioning These workers showed that acute hypoxæmia pro duced by the breathing of pure nitrogen caused a marked pressor rise followed by a fall of blood pressure On substituting air for nitrogen a second pressor rise occurred which was frequently greater in magnitude than the primary pressor effect The collection of adrenal venous blood showed that there was increased secretion of pressor substances during the hypoxæmic phase However the re injection of this blood during the depressor phase of acute hypoxæmia or the injection of adrenaline itself did not cause a rise of blood pressure Only if this blood was re injected into the animals during air breathing at control mean pressures was any pressor effect demonstrable They concluded that the adrenal secretion played little part in the hypoxæmic pressor response but played a major role in the post hypoxæmic secondary rise Mathison (1911) earlier ascribed the post hypoxæmic pressor response to revitalization of the centre by the improvement of the oxygen supply Van Loo and co workers have thus obtained results which suggest that the catechol secretion of the adrenal gland may be of considerable importance in these circumstances

Sino aortic Reflexes and the Maintenance of Blood Pressure After Splanchnic Nerve Section

Ludwig (1866) showed that the blood pressure of the rabbit fell 30–50 mm when the splanchnic nerve was cut On sectioning the other splanchnic nerve however the blood pressure fell only a further 10 mm Hg By stimulation of the peripheral end of the splanch nic nerve the blood pressure could be restored to normal Ludwig appreciated fully the contribution made by the splanchnic nerves to the total peripheral resistance When he discovered the action of the depressor nerve on the cardiovascular system (Cyon & Ludwig 1866) he suggested that the vasodilation so produced was almost wholly splanchnic Grutzner & Heidenhain (1878) disproved this opinion by obtaining a fall of systemic pressure on stimulating the depressor nerve in animals in which the aorta was clamped above the level of the coeliac axis Sollman & Pilcher (1912) confirmed this Porter & Beyer (1900) cut the nerve roots supplying the splanchnic fibres and were still able to evoke reflex hypotension by depressor nerve stimulation Stelling (1867) found that after upper thoracic section of the spinal cord (T_3) hypotension no longer occurred when the de pressor nerve was stimulated but wrongly concluded that the vessels of the head and neck did not normally participate in the reflex vasodilatation

Izquierdo & Koch (1930) found that in the rabbit with the abdomen closed bilateral splanchnic section lowered the systemic blood pressure by only 30% If however the sino aortic nerves had been previously cut the fall of blood pressure amounted to some

70% Kremer & Wright (1932) investigated this phenomenon in cats The splanchnic nerves on each side were exposed and loose ligatures placed round them The ends of the thread were brought out through the wounds which were then stitched up The subsequent division of these nerves was effected by pulling vigorously on the threads In half the animals studied division of both splanchnic nerves caused no fall of blood pressure whatever and in the remaining half the fall was usually much less than 20% The failure of bilateral splanchnic section to cause hypotension could be explained by (1) absence of initial vasomotor tone in the vessels (2) rapid recovery of tone in the denervated vessels or (3) compensatory vasoconstriction elsewhere The first was improbable because of the height of the initial blood pressure and because volume plethysmography of the spleen revealed that a marked increase of splenic volume occurred on section of the nerves Kremer & Wright studied the effect of sino vagal inactivation on the response to see whether they could influence the supposed phenomen of compensatory vasoconstriction The vagi were cut and both common carotid arteries were occluded They regarded this as an adequate degree of inactivation of the buffer nerves They cite systemic blood pressures of 215–270 mm in six animals and it seems reasonable to suppose that the buffer nerves were doing very little In these animals splanchnic section caused a progressive and extensive fall of blood pressure In six experiments the initial levels of blood pressure were 250 245 250 270 215 and 240 mm Hg the final levels (reached about twenty minutes after splanchnic nerve section were 140 105 120 120 105 and 110 mm Hg The average extent of the fall was 130 mm or just over 50% The great difference between their results and those of Izquierdo & Koch is in the rate of fall of blood pressure Izquierdo & Koch in Fig 2 of their paper show that the fall is very rapid being complete in about a minute We feel that the reason for the difference might lie in the method of section used by Kremer & Wright—this sudden drag on the ligatures must have caused considerably mechanical stimulation of the peripheral splanchnic fibres supplying the adrenal glands Kremer & Wright state however that the same results were obtained in one animal in which the adrenals were removed prior to the splanchnic section

Kremer & Wright suggested that compensatory vasoconstriction took place after splanchnic nerve section in animals with intact buffer nerves which accounted for the absence of marked fall in the blood pressure They anticipated that the skin would be the main site of this reaction and that after denervation of the skin splanchnic nerve section would lower the pressure markedly even in the buffered animal This expectation was only partially realized In one experiment for instance nerves were cut the femoral arteries were tied and the skin was completely removed from the trunk forelimbs and part of the neck Both splanchnic nerves were prepared and the cat had an initial blood pressure level of 175 mm Hg After splanchnic section the pressure fell only to 145 mm Hg They were forced to conclude that the muscles were the main regions responsible for compensatory vasoconstriction

Venomotor Tone

The veins are supplied by vasomotor fibres It is probable that the effects of sym pathetic vasoconstrictor discharge on the venomotor tone are of the greatest significance It is very likely that the importance of these effects lies in the modifications of venous

capacity which they induce rather than in the changes of resistance to flow to which they may give rise (Landis & Hortenstein 1950) The measurement of venous pressure central or peripheral gives no indication whatever of the nature of the changes in veno motor tone in response to aortic nerve stimulation and though the older literature abounds with reports of such studies it is not worth considering here

Heymans Bouckaert & Dautrebande (1930 1931) showed that perfused innervated segments of the mesenteric veins constricted when the common carotid arteries were occluded and conversely dilated when the carotid sinus pressure was raised Similar observations were made using perfused innervated segments of the colic vein by Fleisch (1930) and other confirmatory results were published by Gollwitzer Meier & Schulte (1931) Recently Alexander (1954) has reported similar findings He has pointed out that the splanchnic venous system may be constricted by sympathetic activity in response to sino aortic reflexes and as a result blood is displaced in the direction of the heart When the venous pressure is high however the distensibility of the system increases so as to serve as an effective reservoir taking up or discharging significant quantities of blood in response to variations of sympathetic activity In a further paper Alexander (1956) claims that a rise in central venous pressure itself evokes a reflex veno dilatation The afferent pathway of this reflex is vagal for the effect is lost after vagotomy The efferent pathway is however via sympathetic vasoconstrictors for the reflex response is not abolished by atropinisation The reflex venodilatation was produced by obstruction of the inferior vena cava in his experiments and the receptors responsible must therefore be in the veins themselves Alexander has argued that if it were not for this reflex effect an increased venous return to the right heart which produced an increased central venous pressure would increase diastolic filling and hence increase the cardiac output Other things being equal an increased cardiac output would in turn increase systemic pressures and tend to augment venous return thereby further augmenting cardiac output (Alexander) This (somewhat questionable) sequel of events is nevertheless prevented by (*a*) sino aortic buffer reflexes which slow the heart and dilate the peripheral vasculature (*b*) the veno venous reflex described above Rashkind and co workers (1953) in open chest dogs collected the venous return from both venæ cavæ and diverted it into a reservoir from which it was pumped at a constant rate into the right atrium The technique allowed continuous recording of venous return and permitted the measurement of volumes of blood displaced from the dog s vascular system into the reservoir or pooled in the vascular system Stimulation of the sinus nerve caused a reduction in T P R and a reduction in the venous return associated with pooling of the blood in the animal This pooling they reasonably ascribe after a full discussion to increase in the capacity of the post arteriolar vessels (notably the veins) due to a reflex reduction of venomotor tone They point out themselves that the preparation required for these experiments severely compromises the state of the animal nevertheless their results are of great interest and fit in well with the evidence presented above obtained on animals in more normal conditions

Cerebral Asphyxia

The discovery of the function of the sinus nerves provided an explanation of François Franck s observation that a rise of pressure in the cephalic circulation induced brady cardia He had attributed this to a direct effect on the medullary centre Hering (1927)

Koch (1931) Heymans (1929) and Florey Marvin & Drury (1928) all showed that a rise of pressure in the isolated head or cephalic circulation caused bradycardia and systemic hypotension (Fig 31) only if the sinus nerves were intact Figure 32a shows that a rise in the blood pressure of a donor dog (A) (induced by adrenaline) which perfuses the isolated head of a recipient dog causes no effects on the systemic blood pressure of dog (B) The head of dog (B) was connected with its trunk only by the spinal cord The sinus and vagus nerves were cut

On the other hand extreme systemic hypotension may stimulate the vasomotor centre directly by causing asphyxia of the medulla (Traube 1863 Thiry 1864, Fredericq 1882 Gley & Quinquaud 1923 Stewart Pike & Guthrie, 1908, Mathison 1911 Gasser &

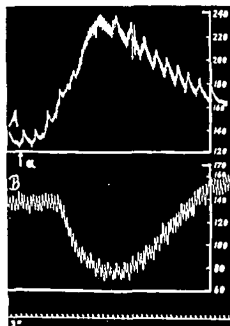
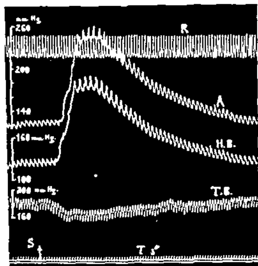


FIG 31 Isolated head of dog B perfused by means of dog A Spinal cord connecting only head B and body B
A = blood pressure of dog A
B = blood pressure of body dog B
a = intravenous injection of 0 1 mg adrenaline to dog A Hypertension dog A and head B induces drop of arterial pressure in body dog B There is little evidence of brady cardia as the vagi are cut in this preparation —(C Heymans (1929) *Arch int Pharmacodyn* 35 307)

Loevenhart 1914 Anrep & Starling 1925 Eyster & Hooker 1907 Binet & Gayet 1929*a* Heymans & Bouckaert 1928 Nowak & Samaan 1935) Fig 32b shows a record obtained by Nowak & Samaan The head of a recipient dog (B) is connected with its trunk only by the spinal cord The sinus and vagus nerves have been cut The head is supplied by the circulation of a donor dog (A)—the cephalic circulation is deliberately limited by clamping one carotid anastomosis and partly occluding the other As a result the medullary centres of the head of (B) are partly asphyxiated and the systemic blood pressure of the trunk is high On injecting adrenaline into the circulation of the donor dog the rise of systemic pressure in dog (A) causes a rise in the cephalic blood pressure of (B) which relieves the medullary asphyxia and the systemic blood pressure of (B) falls as a result of this (cf Fig 32a)

Leyden (1886) Naunyn & Schreiber (1881) and Eyster (1906) found that a rise of intracranial pressure caused initial bradycardia followed by a short phase of cardiac acceleration which in turn gave place to extreme bradycardia At the same time the

systemic blood pressure rose considerably and remained raised for some 40–60 seconds before a terminal decline ensued The origin of the changes of cardiac rate has been variously attributed to (1) mechanical direct excitation of the medullary centres (2) bulbar anæmia (3) the rise of systemic pressure



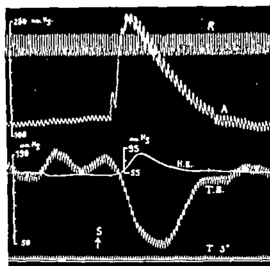


FIG 32a Effect of adrenaline on the vasomotor centre after section of the vago-depressor and carotid sinus nerves (dog B) Method of the isolated perfused head with spinal cord intact
R = stethogram of the trunk of dog B
A = systemic blood pressure (femoral artery) of the donor A which perfuses the head of dog B
H B = perfusion pressure in the isolated head of dog B recorded by a manometer connected to the thyroid branch of the perfusing carotid artery
T B = blood pressure of the trunk of dog B (femoral artery the only connection between the head and the trunk being the spinal cord
S = intravenous injection of 0 05 mg adrenaline into the donor dog A which perfuses the head of B
T = time record in 3 seconds Note the slight fall in the blood pressure of trunk B —(S J G Nowak and A Samaan (1935) *Arch int Pharmacodyn* 51 463)

FIG 32b Effect of adrenaline on the vasomotor centre after section of the vago-depressor and carotid sinus nerves (dog B) Method of the isolated head with spinal cord intact The circulation in the head of dog B is reduced by clamping one artery and partially occluding the other perfusion artery
R = stethogram of the trunk of dog B
A = blood pressure of dog A which perfuses the head of dog B
H B = perfusion pressure of the isolated head of dog B
T B = blood pressure in the trunk of dog B
S = intravenous injection of 0 05 mg adrenaline into the donor A which perfuses the head of B—marked fall of blood pressure in body B
T = time record in 3 seconds —(S J G Nowak and A Samaan (1935) *Arch int Pharmacodyn* 51 463)

Heymans (1928) examined this last possibility The intracranial pressure of a dog was raised via an Eyster cannula (inserted under the dura) connected with a reservoir of Ringer Locke solution kept at 38°C A rise of intracranial pressure caused the usual sequence of changes in the cardiac rate initial bradycardia quickly followed by a short period of tachycardia which in turn gave place to marked bradycardia On lowering the

intracranial pressure the bradycardia persisted for some seconds before a normal tempo was resumed Both carotid sinuses were then denervated and the experiment was repeated The same sequence of changes in the cardiac rate was observed Heymans concluded that raised intracranial pressure caused asphyxia of the centres which were thus affected directly

Harvey Cushing (1902) devoted his attention more particularly to the vasomotor and respiratory effects of raised intracranial pressure If the intracranial pressure was raised abruptly he noted that the respiration ceased but the systemic blood pressure climbed to a level above that of the cerebrospinal fluid whereupon respiration was resumed If the intracranial pressure was raised slowly the systemic pressure showed a similar rise with the result that respiration continued throughout in spite of the very high intracranial pressures which were finally attained Observing the cranial contents through a trans parent window in the skull he noted the appearance of the superior longitudinal sinus throughout the course of these events As the intracranial pressure neared that of the systemic pressure the superior longitudinal sinus diameter wavered thinned and then collapsed The brain substance blanched when the systemic pressure was exceeded although the veins of the gyri remained blue and full Cushing attributed the rise of systemic pressure caused by the above procedure to the direct effect of the raised pressure on the medullary centre unlike Naunyn & Schreiber (1881) who had ascribed it to reflex effects aroused by stretching of the dura mater Eyster (1906) obtained similar changes of systemic blood pressure by the same procedure and drew further attention to the dyspnoeic and periodic changes in the respiration Guernsey Weisman & Scott (1933) re examined the experimental results of raised intracranial pressure with a view to seeing whether the newly discovered sinus reflexogenic zones played any role They believed that the sinus zones could give rise to pressor impulses and thus act as an amphotropic mechanism as had been claimed by Danielopolu *et al* (1927) However they found that the results of raised intracranial pressure were identical whether the sinus nerves were intact or not and also proved that stimulation of the sinus nerve during the period of systemic hypertension caused depressor effects which were sometimes even more powerful than those seen in the normal animal

The effects of raised intracranial pressure have again been studied recently by Rodbard & Saiki (1952) Rodbard *et al* (1954) and Rodbard & Stone (1955) Rodbard & Saiki found that a sudden rise of intracranial pressure in the chick caused systemic hypertension They attributed this to the release of a humoral substance which they claimed resembled noradrenaline in its pharmacological properties They found that the sudden production of a negative pressure in the cranium on the other hand caused systemic hypotension *They advanced the hypothesis that these changes in systemic blood pressure were reflexly* evoked by the excitation or inhibition of pressoreceptors situated inside the cranium These pressoreceptors are believed by them to be responsive to differences in the relative pressure between that in the vessel and that in the cerebrospinal fluid A rise in intra cranial pressure they regard as artificially simulating a fall in cephalic blood pressure They suggest that these hypothetical receptors guard the cerebral blood supply if the cerebral blood pressure falls reflex systemic hypertension thus maintains an adequate blood supply to the brain Rodbard & Stone (1955) have extended their studies to the dog A rise of intracranial pressure to 200 mm Hg caused a rise of diastolic pressure

within one second and a rise of mean pressure from 115 mm Hg to 155 mm Hg in eight seconds The usual result which followed (if the raised intracranial pressure was continued) was a maintenance of this raised systemic pressure for another eight seconds followed by a secondary rise which occurred quite sharply to a systemic pressure of about 215 mm Hg This final level of pressure exceeded that of the c s f and was well maintained until the c s f pressure was released after about forty seconds They attribute the initial rise of systemic pressure to vasomotor discharge and the secondary rise to a release of adrenal hormones Section of the spinal cord in the cervical region abolished the hypertensive responses They argue that the rapid onset of the response of the diastolic pressure is in favour of its being due to causes other than asphyxia of the vasomotor centre and again refer to the intracranial pressoreceptor mechanism We are not inclined to favour their hypothesis The initial effect of a slight rise of systemic pressure caused by raised intracranial pressure may be mechanical Thus when the common carotid arteries are occluded after the carotid sinuses are denervated there is often a rise of a few mm Hg of the mean systemic pressure which is attributed to the reduction of the capacity of the cardiovascular system If this initial early effect is thus explained their other findings are in harmony with the usual theory of asphyxial excitation If these intracranial pressoreceptors play any role in guarding the cerebral blood supply by causing systemic hypertension it must be a very modest one Thus occlusion of both common carotid arteries (if the carotid sinuses are denervated) together with one vertebral artery does not commonly cause a rise of systemic pressure of more than 5–10 mm Hg Rodbard & Saiki claim that the results of Taylor & Page (1951) support their views Taylor & Page found that when the intracranial pressure was raised in a dog s head already subjected to complete cerebral anæmia the systemic hypertension which occurred was greater than that seen when the cerebral anæmia occurred alone

We reiterate that the powerful systemic responses seen in these circumstances are referable mainly to asphyxia of the medullary centres Other minor effects may well be due to abnormal stimulation of nerve endings in the dura caused by stretching or deformation when positive or negative pressures of 200 mm Hg are exerted thereon

Chapter 8

THE MECHANISM OF ACTION OF THE BLOOD PRESSURE ON THE BARORECEPTORS

KOCH referred to the sino aortic nerves as Pressorezeptorische Nerven Never theless the true stimulus to the nerve ending is the displacement of the wall in which it lies Sollman & Brown (1912) unwittingly observed this when they found that traction of the cephalic end of the common carotid artery caused bradycardia Budde (1926) too found during operations in man that traction on structures in the vicinity of the bifurcation caused systemic hypotension and bradycardia Hauss Asteroth & Kreuziger (1949) were the first to show beyond doubt that the prevention of expansion of the sinus wall abolished

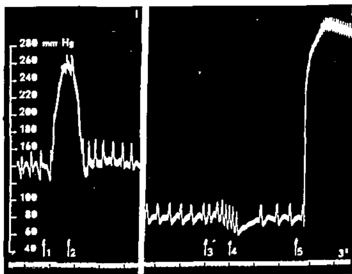


FIG 33 Dog 27 kg Anaesthetized with morphine-chloralosane Both vagi aortic nerves cut Registration of blood pressure at femoral artery
↑ 1 Clamping of carotid arteries
2 Declamping of carotid arteries
Between I and II Infiltration of carotid sinus areas with 0 25 c c 1 noradrenaline 1
3 Clamping of carotid arteries
↑ 4 Unclamping of carotid arteries
↑ 5 Section of carotid sinus nerves —(C Heymans)

the sinus reflexes induced by a rise of endo sinus pressure A cannula carrying a balloon of condom rubber was introduced into the sinus and connected to a mercury manometer The pressure in the balloon was raised and the usual systemic hypotension was seen The sinus was then surrounded by either a plaster of Paris cast or by lead rings which prevented its expansion A rise of *endo* sinus pressure was now ineffective in causing reflex responses These reappeared however when the cast was removed (see also Wakerlin *et al* 1954)

Palme (1936 1943 and 1951) showed that the local application of adrenaline (1 in 1 000) to the wall of the sinus of the rabbit hare or dog caused reflex hypotension but attributed the reflex to the stimulation of the nerve endings or nerve fibres by the drug itself Meurer (1949) observed the same phenomenon in man and claimed it to be due to chemoreceptor stimulation by adrenaline

Heymans & van den Heuvel Heymans (1950 1951 Heymans *et al* 1953*a* *b*) showed that this local action of adrenaline could be simulated by a large variety of drugs possessing only one common property—the ability to cause contraction of smooth muscle Systemic hypotension produced by the local application of such vasoconstrictor drugs was abolished by section of the sinus nerve and was therefore reflex (Fig 33) (See Heymans 1952 1953 1955)

Landgren Neil & Zotterman (1952) confirmed the findings of Heymans showing that adrenaline noradrenaline or vasopressin applied to the sinus wall caused an increase of impulse traffic in the baroreceptor fibres (Fig 34) It was noticeable that the great majority of this impulse increase occurred in the fibres which discharged with low spike height Sodium nitrite which relaxes smooth muscle reduced the impulse traffic in the sinus nerve when locally applied to the sinus

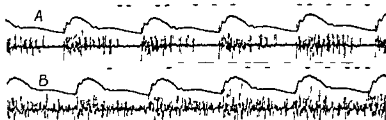


FIG 34 Action potentials from the carotid sinus nerve of the dog Blood pressure registered from the lingual artery Spontaneous respiration (air) Time 25 cycles/second
A Control Mean blood pressure 145 mm Hg
B Four minutes after local application of 0 25 ml 1 adrenaline HCl ($\frac{1}{1000}$) Mean blood pressure 145 mm Hg—(S Landgren E Neil and Y Zotterman (1952) *Acta Physiol Scand* 25 24)

De Vleeschhouwer Martini & Callıauw (1953) obtained similar effects by the topical application of these drugs to the aortic arch

Heymans & Delaunois (1953) and Heymans Delaunois & van den Heuvel Heymans (1953) showed that adrenaline or noradrenaline caused contraction decreased distensibility and increase of the active smooth muscle tension of the arterial wall in the isolated carotid sinus preparation Priscoline had the opposite effects They stated that any drug which caused contraction and increased active tension of the smooth muscle of the wall and lowered its distensibility would thereby modify the excitability of the baro receptors to any given stimulus provided by the blood pressure Landgren (1952) claimed that the local application of adrenaline to the isolated sinus preparation of the cat caused contraction of the sinus wall and produced effects on the distensibility which varied with the sinus pressure At low endosinus pressures the distensibility was decreased by adrenaline at high pressures it was increased by the drug Landgren pointed out that adrenaline must cause a decrease and not an increase in the total tension of the sinus wall provided that the endosinus pressure was unaltered if one assumes that the law of Laplace applies here Thus Burton (1951) stressed that Laplace s law defined the equilibrium conditions in a blood vessel —

$$T = P \times R$$

where T is the total tension P the pressure and R the radius As adrenaline contracts

the wall R is smaller for the same endosinus pressure and T must therefore decrease Landgren analysed the changes which took place in the wall and concluded that the wall consisted of passively elastic elements and contractile or muscle elements The increase

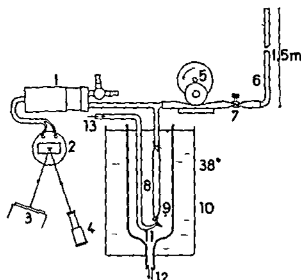


FIG 35a Schema of method for recording pulsatile distensibility of arterial wall of carotid sinus and common carotid artery
1 Device (pressure transducer) for measuring pressure and pulsatile distensibility
2 Galvanometer
3 Photokymograph
4 Light
5 Device for pulsations in artery
7 Regulation screw
8 Isolated carotid sinus—artery
9 Tyrode solution of bath
10 Thermostat
11–12 Tube for inflow and outflow
(C Heymans A L Delaunois and Rovati (1957) *Arch int Pharmacodyn* 109 245)

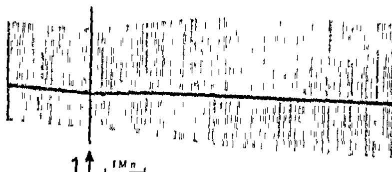


FIG 35b Distensibility of isolated carotid segment shown in Fig 35a At I noradrenaline added to the Tyrode The pulsatile pressure variation in the artery segment increases showing a reduction in the pulsatile distensibility of the arterial wall

in small baroreceptor spikes which was evoked by the topical application of adrenaline he attributed to the small baroreceptor endings being placed in series with the circular muscle fibres in the media The lack of response of the large baroreceptors he in turn explained by postulating their arrangement in parallel to the muscle fibres lying in the adventitia He expressed the opinion that the marked reflexogenic effect of the topical application of adrenaline was a further illustration of the importance of the small baro receptors in controlling the blood pressure This has long been the view of Zotterman—the large baroreceptors have even been claimed by him to do nothing

In considering this point we must concede that the small baroreceptors which are so much more numerous are indeed likely to be of the greater importance. We do not however feel that the evidence advanced encourages a belief in a separate arrangement of two types of receptors. It is remarkable that there should be so few histological reports of endings in the media if the preponderance of small baroreceptors is found there.

Heymans, Delaunois & Rovati (1956) have used the arrangement shown in Fig. 35a to investigate further the changes in distensibility caused by noradrenaline. The pump delivers a pulsatile stimulus and the pressure recorded in the system is recorded photographically. Fig. 35b shows the effect of adding noradrenaline to the Tyrode solution which bathes the preparation. The drug increases the pressure expansion caused by the

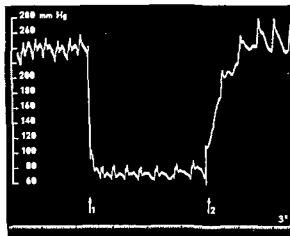


FIG. 36. Dog. The normally innervated baroreceptive carotid sinuses are empty, thus without pressure. Vagi aortic nerves cut. Systemic arterial pressure at 240 mm Hg.
1. Local application to both carotid sinuses walls of 0.2 mg noradrenaline. The systemic blood pressure drops reflexly from 240 to 70 mm Hg.
2. Section of both carotid sinus nerves: rise of systemic arterial pressure from 70 to 260 mm Hg.—(C. Heymans and A. L. Delaunois, *Proc. Soc. exp. Biol. Med.* (1955), 89, 597.)

pump stroke and therefore reduces the *pulsatile expansion or distensibility*. The authors therefore discard the idea that the baroreceptors are stimulated by the drug due to its causing an increase in the pulsatile expansion of the vessel wall. Heymans & Delaunois (1955) ligated all branches of both carotid sinuses and opened the common carotid arteries proximal to the bifurcations. The sinuses were therefore empty and pulseless. The systolic blood pressure as a result was high. Topical application of noradrenaline induced reflex hypotension (Fig. 36), which was abolished by section of the sinus nerves. These results show that an increase of intra mural tension stimulate the baroreceptors. Heymans and his colleagues stated that the effectiveness of the baroreceptor mechanism would be dependent on the state of tension in the wall itself.

There are perhaps simpler ways of considering the mechanisms involved. If it be supposed that the baroreceptor is a stretch receptor this does not necessarily commit us to believing that it must be stretched only by increasing the circumference of the sinus wall, as must be usually the case with the arterial expansion produced by the pulse. The nerve endings are after all three dimensional and it is equally likely that they can be distorted by longitudinal stretching or indeed by any mode of deformation or distortion.

Such an interpretation would allow the several methods of stimulating baroreceptors to be grouped under one heading—i.e. methods of causing deformation or distortion

Thus tugging on the sinus or stretching of the sinus by the weight of cannulæ etc have long been known to cause stimulation of the nerve endings Mechanical pressure on the sinus causes deformation of the endings Pulsatile expansion stimulates the endings—only if expansion is prevented is the pressure rise with each pulse ineffective Longitudinal tension in the vessel wall which has not been considered so far as Green points out (1954*b*) is also present If a piece of artery is cut from its surroundings and removed *from the body it shrinks in length As the artery contains no longitudinal muscle fibres* (Maximow & Bloom 1937) it must be in a state of longitudinal elastic tension maintained by non muscular elements unless we are to suppose that the so called circular muscle is really helical Green has shown that longitudinal stretching of the common carotid artery increases the baroreceptor discharge of a fibre in the common carotid nerve (1954*b*)

The action of drugs which stimulate smooth muscle may be supposed to cause local deformation or distortion of the adventitia in the vicinity of the nerve endings The media must in any case be attached to the adventitia and if the muscular elements of the media contract there must be deformation at these adjoining surfaces

Whatever be the final explanation the important point resulting from these experimental results of Heymans is that changes in the wall itself may affect the sensitivity of the baroreceptors The drugs are merely employed as tools in this respect It is not our belief that noradrenaline or adrenaline circulating in the blood stream in natural circumstances causes any modification whatever in the properties of the sinus wall It can easily be shown (Neil 1952) that 10^{-6} adrenaline does not influence the baroreceptor sensitivity in the perfused sinus In this respect Heymans and his colleagues have been misunderstood by several authors

Heymans has urged that a change in the biological properties of the wall might be an important initiating factor in the development of hypertension McCubbin *et al* (1956) *have recently studied the baroreceptor discharge in dogs suffering from renal hypertension* Such animals have a mean pressure of about 250 mm Hg but the baroreceptors fire phasically with each pulse In normal animals with a mean pressure of this order the baroreceptor discharge is continuous Hence the baroreceptor discharge is less than might be expected This is further borne out by results obtained by perfusing the sinus at various pressures In the renal hypertensive dog the baroreceptors may show only sparse discharge even at mean pressures of 120 mm despite there being a pulsatile pressure of 50 mm occurring about this mean In normal dogs obvious phasic discharge occurs in these perfusion conditions (Fig 37) The baroreceptor mechanism seems to be set at a higher level in established hypertension Whether this is due to an alteration in the mechanical properties of the wall remains or whether it represents a state of adaptation of the nerve endings is still unanswered Further work is needed to examine the characteristics histological and functional of the sinus wall in these conditions In this respect it is wise to point out that the functional characteristics of the sinus wall are almost certain to be different from those of any other part of the arterial tree owing to the sparse and eccentric distribution of muscle in the media of this particular region This must be borne in mind in interpreting results of distensibility measurements made in the isolated sinus preparation solely in terms of the properties of the sinus itself

The normal stimulus to the baroreceptor is stretch (or deformation or distortion) phasically produced by pulsatile variations of the blood pressure In this respect the

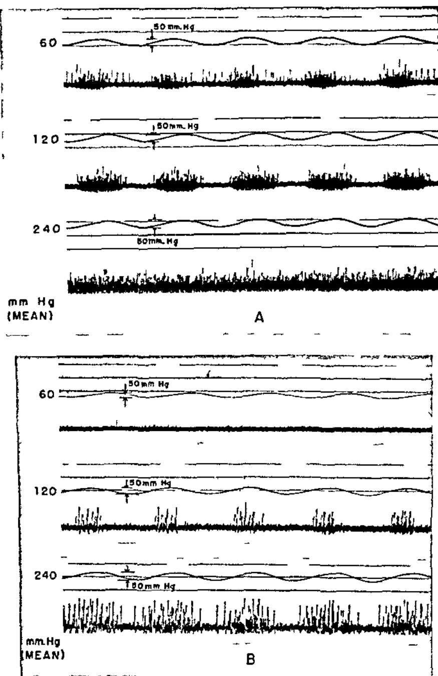


FIG 37 Neurograms from multifiber preparation of carotid sinus nerve of (A) normotensive and (B) hypertensive dog during standard endosinus pressure stimulus Breaks in top reference line at 1 second intervals —(J W McGubbin J H Green and I H Page (1956) *Circulation Research* 4 205)

baroreceptor behaves like any other mechanoreceptor and is sensitive not only to the magnitude of the mechanical stimulus but also to the velocity of its application Presumably deformation of the membrane causes the development of a receptor potential

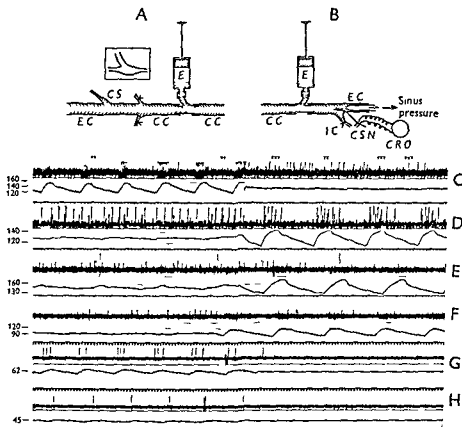


FIG 38 A = the arrangement of cannula and syringe system in the common carotid artery E = elasticity chamber represented by the syringe containing air The plunger of the syringe is heavily greased to make the system leak proof CC = common carotid artery CS = carotid sinus EC = external carotid artery The inset figure shows the shape of the cannula employed B = the type of experiment described in text CSN = carotid sinus nerve IC = internal carotid artery Recording electrodes connected with cathode ray oscilloscope (CRO) Sinus pressure registered from external carotid artery Each film strip shows time (50 cycles/second) sinus electroneurogram and sinus pressure from above downwards C = effect of transition *pulsatile to non pulsatile sinus blood flow at a mean pressure of 140 mm Hg (animal 1)* D = transition from non pulsatile to pulsatile state at mean sinus pressure of 130 mm Hg (animal 2) E and F = both obtained from another animal (animal 3) and show transitions at mean sinus pressure of 150 and 95 mm Hg respectively G and H = both obtained from animal 4 and show transitions at mean sinus pressures of 62 and 45 mm Hg respectively The sinus blood pressure calibrations in mm Hg for each record are shown on the left —(H. W Ead J H Green and E Neil (1952) *J Physiol* 118 509)

which in turn generates the nerve impulse There is no evidence that acetylcholine plays any normal role as a transmitter (Diamond 1955) although it stimulates the baro receptors Bronk & Stella (1932) showed how the single baroreceptor responded not only to a steady endosinus pressure but to a rate of rise of pressure They also showed that

recruitment of extra baroreceptor units could occur with phasic rises of pressure about a given mean There is thus every reason to believe that a pulsatile endosinus pressure should be more effective in exciting baroreceptor discharge than should a steady pressure

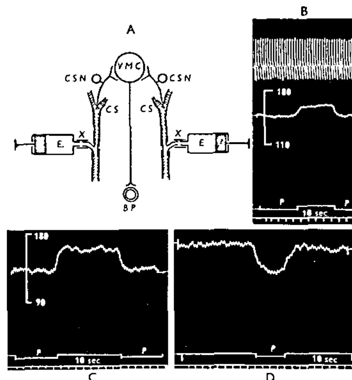


FIG 39 A = scheme of the experiments described in text Both common carotid arteries were cannulated and the cannulæ attached to syringes containing air When the syringes were excluded by clips at the points X and X the blood flow through the carotid sinuses was pulsatile Removal of the clips converted the sinus blood flow to a non pulsatile flow Both sinus nerves were intact and exerted afferent inhibition of vasomotor discharge Changes of peripheral resistance thereby induced caused changes of systemic blood pressure C S = carotid sinus C S N = carotid sinus nerve V M C = vasomotor centre B P = blood pressure B = cat 3 6 kg. sodium pentobarbitone anæsthesia Both aortic nerves cut vagi intact Common carotid arteries cannulated as shown in A Records from above downwards respiration systemic blood pressure signal marker and time in 10 second intervals Note that the systemic blood pressure is maintained at a higher level when sinus flow is non pulsatile (as shown by signal marker) than when it is pulsatile (P) Respiration is unaffected C = cat 3 3 kg. chloralose urethane anæsthesia Aortic nerves and vagi cut Arrangements as in A Note that the systemic blood pressure is higher during non pulsatile sinus flow (shown by signal marker) than that during pulsatile flow (P) D = obtained from the same preparation 30 minutes later During this period the carotid sinuses were exposed to non pulsatile flow The high level of systemic pressure was maintained (cf C) but conversion to pulsatile sinus flow (P) lowered the systemic pressure —(H W Ead J H Green and E Neil (1952) *J Physiol* 118 509)

with the same mean value Curiously however the earlier literature contains two papers in which it is claimed that the reflex effects of each type of stimulus were essentially similar (Barany 1943 Strauss 1940)

Ead Green & Neil (1952) therefore re examined the question Inserting a T cannula into the common carotid artery they connected the stem of the T to an

elasticity reservoir By clipping this connection the corresponding carotid sinus could be exposed to the normal pulsatile pressure of the systemic circulation which was recorded by a condenser manometer connected with a cannula in the external carotid artery The

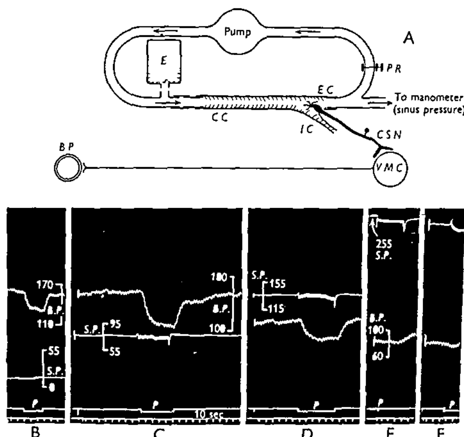


FIG 40 A = scheme of the experiments described in text One carotid sinus was isolated and perfused by a pump An elasticity chamber (E) was placed on the inlet side of the perfusion circuit Sinus pressure was recorded by a mercury manometer Changes of sinus pressure caused reflex changes of vasomotor dis harge and hence systemic blood pressure CC EC and IC = common carotid external carotid and internal carotid arteries CSN = carotid sinus nerve VMC = vasomotor centre PR = resistance on pump perfusion circuit BP = systemic blood pressure B–F = cat 3 4 kg chloralose urethane anæsthesia Right carotid sinus isolated and perfused Left carotid sinus and both aortic nerves cut Records from above downwards systemic blood pressure sinus perfusion pressure signal marker time in 10 second intervals Records show comparison of reflex effects of pulsatile and non pulsatile sinus perfusion at mean pressures of 15 80 135 and 235 mm Hg BP = systemic blood pressure SP = sinus pressure —(H W Ead J H Green and E Neil (1952) *J Physiol* 118 509)

sinus nerve cut centrally was laid on electrodes and by dissection single or few fibre preparations were made for recording As expected such baroreceptors showed phasic activity with the pulse By removing the clip the elasticity reservoir was included in the system and the pulsatile pressure was thereby modified to a steady pressure of the same mean value The impulse activity itself became sensibly steady The frequency of this steady firing never approached that attained in the phasic bursts Moreover it was not

uncommon to find that units which discharged phasically during pulsatile conditions ceased to fire when the endosinus pressure became steady at the same mean value (Fig 38) In further experiments both common carotid arteries were cannulated in the above manner but the innervation of the sinuses was preserved The vagi were cut The systemic blood pressure rose each time that the sinuses were exposed to steady pressure by connecting the elasticity reservoirs (Fig 39) This proves that a pulsatile stimulus of the baroreceptors is more effective than that provided by a steady stimulus represented by a higher mean pressure Finally the reflex effects exerted by sinus perfusion at steady or pulsatile pressures were compared There was no doubt that pulsatile pressures were far more effective (Fig 40) The threshold mean pressure for the steady pressure perfusion was about 70 mm that for the pulsatile pressure was less than 15 mm in the circumstances It follows from such findings that changes in extent or in rate of rise of the pulse pressure may modify the behaviour of the baroreceptors even though the mean systemic pressure has meanwhile shown no change Moreover changes in heart rate may modify the stroke volume and hence the pulse pressure and again alter the baroreceptor discharge even though the mean systemic pressure has remained unchanged Neil (1952) discussed the reflex adjustments to slow hæmorrhage in this light It has long been known that a slow bleeding may be attended by reflex cardiac acceleration and systemic vasoconstriction even though no fall of systemic blood pressure has occurred In such circumstances the cardiac output falls progressively so clearly the blood pressure is maintained by increased peripheral resistance of vasomotor origin This cannot be attributed to the sino aortic reflexes if one believes the baroreceptors to be solely responsive to alterations in mean blood pressure for this has not changed On the other hand the reduction of cardiac output must first express itself as a reduction of stroke volume and this in turn must reduce the pulse pressure The baroreceptor stimulation is correspondingly reduced and tachycardia ensues which further reduces the stroke volume and pulse pressure In this manner it is quite possible to explain progressive vasoconstriction It is of course likely that these sino aortic reflex adjustments are not solely responsible for the vasoconstriction but the role of the cardio pulmonary afferents in these circumstances is as yet obscure (see p 229)

Palme (1943) showed that the stimulation of the sympathetic branches which supply the carotid bifurcation caused a fall in systemic blood pressure similar to that following the local application of adrenaline to the sinus wall which he was also the first to describe Kezdi (1954) has recently confirmed these results By continual stimulation of the sympathetic supply to the carotid sinus he was able to reduce the systemic blood pressure to levels of 80–100 mm Hg at which occlusion of the common carotid arteries did not cause any reflex rise in the systemic pressure He argued that the effect of sympathetic stimulation was due to the induced contraction of the muscular tissue in the sinus wall which stimulated the baroreceptors Landgren (1952*b*) who believes that the small baroreceptor units are situated in the arterial media of the sinus arranged in series with the muscle fibres points out that the sympathetic fibres to the sinus wall may play a part similar to that of the γ efferents to the muscle spindles (Leksell 1945) If we accept this point of view then the mechanism of the sinus baroreceptor control of cardiovascular activity is more complicated than has been previously assumed Thus a fall of blood pressure causes less baroreceptor activity than normally which then causes a greater

sympathetic discharge to the sinus wall and this in turn increases the baroreceptor stimulation Conversely a rise of blood pressure induces reflexly less sympathetic discharge and consequently less baroreceptor activity It is difficult to see how such a mechanism could operate with advantage to the intact organism

Floyd & Neil (1952) tested the claims of Palme very carefully They were unable to confirm that the stimulation of the local sympathetic supply to the carotid sinus caused a fall of systemic blood pressure In further experiments they raised the pressure in a Moissejeff isolated sinus and examined the reflex response Stimulation of the sympathetic supply of the isolated sinus did not modify the reflex response of the systemic blood pressure to a given rise of static pressure in the isolated sinus Finally, they examined the effect of stimulating the local sympathetic nerve supply on the impulse activity of single baroreceptor units responding to the pulsatile pressures produced by the heart in the intact circulation In one instance only did they find that the impulse activity of a baroreceptor unit was increased by the sympathetic stimulation There were many negative results Floyd & Neil concluded that the local innervation of the sinus region by the sympathetic nerves was of little practical importance in modifying the sinus baroreceptor sensitivity It should be remembered that the muscularity of the media in the sinus region is both sparse and eccentric If the sympathetic fibres do cause any effect on the tone of the arterial musculature in this region it is likely to be exerted in adjacent parts of the vessel wall rather than in the sinus itself As a result there may be slight distortion of the sinus which could in turn increase the activity of the receptors themselves

CHAPTER 9

CLINICAL CONDITIONS INVOLVING THE SINO AORTIC BARORECEPTOR REFLEXES

Carotid Sinus Syndrome

IN 1799 Parry reported that strong pressure on one of the carotid arteries would retard the motion of hearts beating with undue quickness and force Similar results were reported by Waller (1862) Both authors attributed their results to the effect of mechanical irritation of the neighbouring vagus nerves Tschermak (1866 1868) independently observed the same phenomenon and noting the swelling of the common carotid artery at the upper border of sternomastoid attributed the bradycardia caused by digital pressure in this vicinity to the transmission of the pressure via this swelling His Vagusdruckversuch based on this observation was used by clinicians throughout the latter part of the last century and although Concato (1870 1872) noted that the most striking results were obtained by pressure over the carotid bifurcation neither he nor his colleagues ascribed any particular significance to this observation The reflex nature of the phenomenon was proved by Hering (1924) whereupon clinical workers paid fresh attention to this region

Koch (1924) was the first to examine the effects of mechanical stimulation of the carotid sinus itself in man In 50 patients he obtained a 25% fall in systemic blood pressure in 28 of them He attributed the systemic hypotension to a vasomotor reflex as it occurred independently of cardiac slowing Hess (1925) confirmed these findings Mehrmann (1925) was the earliest to note the dramatic cardiovascular effects which could be induced by pressure over the carotid sinus of arteriosclerotic patients Wenckebach & Winterberg (1927) reported similar cases—see also Mandelstamm *et al* (1929) Jacobovici Nitzescu & Pop (1929) Danielopolu Marcu & Proca (1928) Regniers (1930) Rossi (1930) Egberts (1932) and Marinesco & Kreindler (1930 1931)

Roskam (1930) related a particularly vivid history of a man 53 years old Armand C In 1929 en mai la femme de notre patient l aidant a mettre un col trop etroit glissa un doigt entre le col rigide et le cou aussitot son mari s affaissa evanoui On examination the patient had a high pulse pressure On strong pressure on the left carotid artery nothing happened but Roskam states that he had hardly touched the region of the carotid sinus itself before the patient became pulseless and apnœic in a faint Suitably revived the patient was placed on hypotensive medication De Brun reported a similar case history (1932) (see Merklen 1934)

Weiss & Baker (1933) made a detailed clinical study of carotid sinus compression in healthy subjects and in patients with cardiovascular disease In 50 subjects mechanical stimulation produced a fall of 10 mm Hg or less in the systemic pressure In patients with hypertension and particularly in those with primary arteriosclerosis without hyper tionsion (36 patients) the fall in pressure caused by sinus compression was more obvious

and was more frequently seen In 15 patients the carotid sinus reflex was hyperactive and 13 of these complained of spontaneous attacks of dizziness and fainting Three main types of cardiovascular response occurred on mechanical stimulation of the sinus

1 marked bradycardia usually but not invariably attended by hypotension
2 profound hypotension without bradycardia
3 changes in the cerebral circulation unaccompanied by obvious systemic hypotension or bradycardia

Weiss & Baker found that partial or complete heart block could be induced by sinus compression in these hyperactive reflex patients They used the term ' carotid sinus *syndrome to describe this type of case In a further paper Weiss and his colleagues* (Ferris Capps & Weiss 1935) studied 32 cases with a history of spontaneous fainting in which mechanical stimulation of the carotid sinus promptly induced manifestations of a similar nature The attacks were not abolished by atropine pilocarpine ephedrine ergotamine amyl nitrite or strychnine Digitalisation increased both the frequency of the spontaneous attacks and exacerbated the severity of those deliberately induced by compression of the sinus The sensitive carotid sinus was denervated surgically in seven of the cases and complete freedom from spontaneous attacks was obtained As might be expected there was no permanent change in either the blood pressure or the heart rate following the unilateral sinus denervation

Takayashu's Disease

In 1908 Takayashu described an unusual syndrome in which the main features were those of a chronic obliterative brachiocephalic arteritis in which the upper half of the body is gradually deprived of its blood supply Until recently this clinical entity was regarded as peculiar to Japan Caccamise & Whitmann (1952) collected reports of 58 cases in Japan and mentioned that the condition had not been observed elsewhere Erik Ask Upmark (1954) in a recent scholarly paper has refuted this point of view and besides presenting three clinical cases of his own has assembled data concerning 25 other cases in Europe and America Ask Upmark notes the extraordinarily high proportion of women in the clinical cases so far observed 27 of the 28 cases to which he refers being women The average age of onset in these cases was 30 years Ask Upmark summarizes the symptoms under five headings (1) those due to ischæmia of the upper half of the body (2) those associated with the development of a collateral circulation (3) those due to a carotid sinus syndrome (4) cardiac symptoms and (5) general symptoms In the present context we may briefly review the symptoms of carotid sinus syncope Shimuzu (1948) was the first to stress the increased sensibility of the carotid sinus in this disease Syncopal attacks are particularly likely to occur on changing the posture of the head or on fingering the carotid sinus region Kouretas & Djacos are credited with the remarkable observation that the sensitivity of the carotid sinus varied with the female period being most marked immediately before during and immediately after the period Ask Upmark suggests that the cicatricial tissue around the carotid sinus rendering the structure less mobile and thus more liable to cause traction on the sinus nerve on moving the head is responsible for the increase in reflex sensibility

In a further paper Ask Upmark & Fajers (1956) have assembled additional evidence from other cases of Takayashu s disease bringing the total number of cases observed outside Japan to forty five

Miscellaneous

Certain authors have claimed that hyperactive carotid sinus reflexes may contribute to the pathogenesis of epilepsy Danielopolu and his colleagues have compared the occasional convulsant effects produced in the dog by faradization of the sinus nerve with the corticomotor reactions seen in the epileptic Danielopolu has proposed that the sinus regions might be denervated in epileptic patients Jacobovici Nitzescu & Pop (1928) removed the carotid body in six epileptic patients in the mistaken belief that it was the seat of origin of hyperactive baroreceptor reflexes but they obtained only temporary improvement in their patients health Merklen (1934) who cites these results also mentions that Lauwers (1930) obtained a certain improvement in ten epileptic patients after removing the carotid body We do not think that there is any point in such operations in epileptic patients Lennox (1933) stated that in 150 cases of epilepsy carotid sinus stimulation did not precipitate a convulsion (see Weiss & Baker 1933)

Pressure on the carotid sinus is one of the best ways of terminating an attack of paroxysmal tachycardia (Bensen 1880 Preisendorff 1880 Regniers 1930*b*) According to Regniers sinus pressure is rarely effective in attacks of extrasystole which he attributes to the vagal origin of many of these attacks

Although angina pectoris has been successfully terminated by mechanical pressure on the sinus region we feel it important to stress that the danger of untoward arrhythmias induced by the manœuvre outweighs any therapeutic effect which it might be expected to exert

Budde (1926) has suggested that section of the sinus nerves might be considered as a therapeutic measure when the systemic blood pressure falls to low levels during cervical operations Koch (1931) strongly opposed this suggestion pointing out that the section of the sinus nerves could have little effect if the low level of the blood pressure were due to general causes As he himself has shown and as Heymans and co workers have confirmed the sinus nerves exert little reflex effect on the blood pressure unless the level of systemic pressure is above 70 mm Hg Hence if the systemic pressure is reduced by surgical shock hæmorrhage or other general causes the sinus nerve endings will be minimally stimulated in any case so that their destruction can hardly be expected to confer any benefit Koch agreed that the blood pressure might be reflexly lowered during operations in the sinus region by traction on the neighbouring structures but suggested that the sinus region might be infiltrated with some local anæsthetic It is to be remembered that the volatile anæsthetics sensitize the baroreceptors (Robertson Swan & Whitteridge 1956) and as a result there may be unduly vivid sinus reflex responses to manipulation of structures in the neck adjacent to the sinus

Burstein *et al* (1949 1950) claimed that the administration of 30–100 units of tubo curarine prevented the reflex response of systemic hypotension and bradycardia induced by digital pressure on the carotid sinus Claude Bernard (1857) had shown that curare prevented the cardiac effects evoked by the stimulation of the vagus Clark (1956) re examined the effect of curare on the responses evoked by carotid sinus pressure In two

patients the administration of 100 units of curare caused either no difference in the cardio vascular response to carotid sinus stimulation or (in one) a very slight reduction Infiltration of the sinus region with 5 ml of 1% hexylcaine completely abolished the reflex response to sinus pressure on that side (see Fig 41)

Sinus Reflexes in Essential Hypertension

Regniers (1930) described five cases of hypertension in which compression of the carotid sinus caused as usual bradycardia and a fall of blood pressure while obliteration of the carotid arteries below the level of the sinus caused no cardiovascular effects He

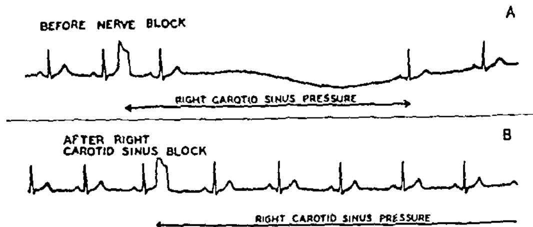


FIG 41 Electrocardiograms obtained from a patient Carotid sinus external pressure before (A) and after (B) block of carotid sinus innervation —(R E Clark (1955) *Anesthesiol* 16 716)

also observed that the bradycardia occurring in normal subjects on release of carotid occlusion did not occur with his patients with high blood pressure and suggested that the carotid sinus did not respond to changes in intra sinus pressure Mies (1932) investigated 97 patients with high blood pressure and found 17 without renal insufficiency in these 17 patients carotid sinus pressure caused the usual response but obliteration of the common carotid arteries caused no rise of blood pressure He also concluded that the raised blood pressure of these patients was due to a disturbance of the carotid sinus and depressor mechanisms so that they ceased to respond to the stimulus afforded by the arterial blood pressure

Pickering Kissin & Rothschild (1936) re investigated the matter in view of the importance of the point and obtained totally dissimilar results They could find no obvious difference in the response to carotid occlusion in hypertensive and normal men There was no foundation for the claims of Mies and Regniers Kezdi (1953) has since shown that the blood pressure rises in patients with essential hypertension when one or both sinus nerves are anæsthetized by the local injection of procaine in the sinus region Moreover experimental studies on chronic renal hypertension have revealed that the sino aortic mechanisms maintain their buffer activity (Matton 1954 McCubbin *et al* 1956) (See Fig 44)

Blood Pressure Regulation and Circulatory Failure (Shock)

As defined by Wiggers shock is a syndrome resulting from the depression of many functions Reduction of the effective circulatory volume and a prolonged fall of blood pressure are the most fundamental contributory causes of the shock syndrome resulting as they do in steadily progressive circulatory failure with eventual collapse A clear understanding of the factors which are responsible for the normal regulation of the arterial blood pressure and the capacity of the circulation is necessary before we can explain the shock syndrome

In normal circumstances the baroreceptor reflexes are probably of prime importance in the compensatory changes which occur in the circulation as a result of a fall of arterial

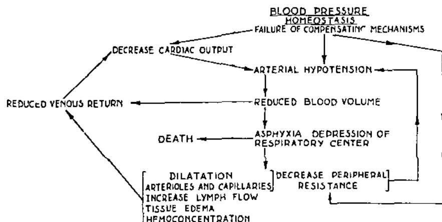


FIG 4 Vicious Cycle in Shock (C Heymans (1950) Introduction to the Study of Blood Pressure Thomas & Co Springfield)

blood pressure due to hæmorrhage or other insults Heymans (1950*b*) has referred to the blood pressure reserve which exists in the normal animal Thus if bleeding occurs the blood pressure tends to fall and the sino aortic inhibition of the vasomotor centre lessens Hence compensatory vasoconstriction which occurs both in arterioles and veins raises the peripheral resistance and diminishes the capacity of the circulation The blood pressure is restored to normal and the venous return is more adequately sustained than might be expected considering the blood loss Such an animal has however encroached upon its blood pressure reserve and will be less able to withstand further bleeding Eventually the point is reached at which blood pressure is preserved at normal or near normal levels only by virtue of maximal activity on the part of the sympathetic arteriolar and venomotor mechanisms further blood loss induces a complete failure of blood pressure homeostasis and leads to a state of irreversible circulatory failure or shock

Whereas the preceding paragraph relates to the effects of hæmorrhage in inducing shock it is well recognized that a number of other factors are capable of causing the onset of this syndrome When it is recalled that the blood pressure is governed by both cardiac output and peripheral resistance it is clear that either heart failure or peripheral circulatory failure may be the initiating factors Once any component of the system is seriously

disturbed a vicious cycle tends to be set up which leads to further disorganization of the regulatory mechanisms of arterial blood pressure and circulatory capacity The main pathways which lead to the same end result of circulatory failure are illustrated in Figure 42

The avoidance of conditions which favour the disturbance of the baroreceptor regulatory mechanisms of circulatory capacity and blood pressure is the most rational procedure in preventing the development of shock Of the narcotic drugs barbiturates should be used sparingly the use of high spinal anæsthesia in patients subjected to traumatic operation would seem to be unwise Similarly the administration of ganglio plegic drugs should be restricted The prevention of shock is also aided by prompt restoration of the blood volume In shock due to vasomotor or cardiac failure therapy with sympathico mimetic drugs *such as noradrenaline and ephedrine may be useful* Vasomotor and respiratory failure due to barbiturate poisoning may be specifically treated by giving picrotoxin Oxygen administration may counteract incipient cerebral anoxia due to failure of circulatory and respiratory central mechanisms However once the progressive stage of shock has supervened the various therapeutic measures available at the moment are ineffective because irreversible changes in physiological functions have occurred A better knowledge of the nature of these functional alterations would accelerate progress in the treatment of circulatory failure and shock

CHAPTER 10

NEUROGENIC HYPERTENSION

THE discovery by Hering that the arterial blood pressure rose steeply after acute denervation of the sino aortic areas led naturally to the hypothesis that Essential Hypertension seen in man might be due to some dysfunction of the baroreceptor reflexes Such an idea could only be tested by preparing chronic animals for survival after complete interruption of their sino aortic afferents The hæmodynamics and circulatory responses of such beasts could then be compared with those characterizing Hyperpiesia Unfortunately the radical denervation of the aortic area necessitates bilateral vagotomy and vagotomized animals do not survive (Haighton 1795 Cruickshank 1795 Legallois 1812 Philippeau 1885 Tournade 1913 Sharpey Schafer 1919) The animals vomit frequently and usually succumb on the second or third day after the operation On autopsy the larynx is generally obstructed by secretions and the trachea and lungs contain vomitus Only by making a preliminary gastrostomy and œsophagostomy were Pavlov (1895 1896) and his pupils Cashcovsky (1899) and Cheshcov (1902) able to obtain survival of vagotomized dogs for months (see Pavlov 1910) Samaan (1934) who made a most careful study of the effects of cutting some or all of the vagal components concluded that the failure of animals to survive total vagotomy could usually be ascribed to their developing aspiration pneumonia

The rabbit which possesses separate aortic nerves offers anatomical advantages over the other laboratory animals which are however partially offset by the extreme lability of the arterial blood pressure in this species

The dog though suitable as a chronic survival animal offers the most formidable difficulties of any of the common laboratory animals to selective denervation of the aortic afferent fibres as these course usually in the cervical vago sympathetic trunks themselves Hence it is necessary to compromise by cutting as many of the vagal afferents as possible without destroying too many of the efferent fibres One may therefore fail in two ways—an inadequate deafferentation in which case the dog does not develop enduring hypertension or excessive destruction of the efferents which leads to intractable vomiting inanition and the eventual death of the animal

Thomas (1944) divided both sinus nerves stripped the nerve fibres from the common carotid and its branches in the region of the bifurcation and painted the sinus region with 5 % phenol The left cervicovagal trunk was sectioned and a two centimetre length was excised The medial third of the right cervical trunk was cut and excised for two centimetres leaving the remainder of the right vagus carrying a sufficient number of efferent fibres She recommended that the operations required were done in stages

There is an extensive literature on neurogenic hypertension produced by denervation of the carotid and aortic vaso sensory areas

disturbed a vicious cycle tends to be set up which leads to further disorganization of the regulatory mechanisms of arterial blood pressure and circulatory capacity The main pathways which lead to the same end result of circulatory failure are illustrated in Figure 42

The avoidance of conditions which favour the disturbance of the baroreceptor regulatory mechanisms of circulatory capacity and blood pressure is the most rational procedure in preventing the development of shock Of the narcotic drugs barbiturates should be used sparingly the use of high spinal anæsthesia in patients subjected to traumatic operation would seem to be unwise Similarly the administration of ganglio plegic drugs should be restricted The prevention of shock is also aided by prompt restoration of the blood volume In shock due to vasomotor or cardiac failure therapy with sympathico mimetic drugs such as noradrenaline and ephedrine may be useful Vasomotor and respiratory failure due to barbiturate poisoning may be specifically treated by giving picrotoxin Oxygen administration may counteract incipient cerebral anoxia due to failure of circulatory and respiratory central mechanisms However once the progressive stage of shock has supervened the various therapeutic measures available at the moment are ineffective because irreversible changes in physiological functions have occurred A better knowledge of the nature of these functional alterations would accelerate progress in the treatment of circulatory failure and shock

In some cases however even then the high pressure tended to subside indicating that there were still some depressor fibres active in the remaining vagus nerve

Nowak & Walker (1939) Nowak (1940) and Thomas (1944) using dogs confirmed Boyd & McCullagh s findings Thus the main elevation of blood pressure occurred within 2–3 weeks after the operation Thomas (1944) believed tachycardia to be a primary factor in neurogenic hypertension thus produced and suggested that the lability of blood pressure depended on the variable heart rate This would distinguish neurogenic and renal hypertension In two dogs with persistent neurogenic hypertension constriction of the renal artery using the Goldblatt technique did not further raise the blood pressure although in both animals the hypertension changed into the malignant type (Thomas 1944)

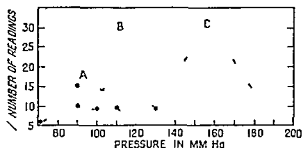


FIG 43 Chronic hypertension in the rabbit following division of the sino-aortic nerves
A = Normal range of blood pressure in rabbit (mean 90 mm)
B = Range of B P after division of sino-aortic nerves on *one* side (mean 110 mm)
C = Range of B P after division of sino-aortic nerves on both sides (mean 155 mm) —(Kremer Scarff and Wright (1933) *Brit J exp Path* 14 281)

The cold pressor test gave variable results in dogs with neurogenic hypertension (Thomas & Warthin 1940) The tolerance of hypertensive dogs to sustain graded hæmorrhages was the same as that of normal dogs This latter observation is somewhat surprising in view of the marked instability of the cardio vascular system in animals with their vaso sensory areas denervated

The morbid anatomical changes following the production of neurogenic hypertension have attracted a good deal of attention Nordmann (1929) examining the animals of the original series of Koch & Mies (1929) showed cardiac hyperplasia fibrotic changes in the heart muscle aortic and pulmonary muscular sclerosis and atrophy of renal glomeruli with or without interstitial fibrosis Kremer Wright & Scarff (1933) found moderate left ventricular hypertrophy but were unable to reach definite conclusions Boyd & McCullagh (1938) also observed left ventricular hypertrophy with variable degrees of myocardial fibrosis Gross changes were found in the aortic media especially in the aorta ascendens with hyalinization and calcification The degree of myocardial fibrosis and degeneration of the aorta could be correlated with the duration and extent of the hyper tension Goormaghtigh (1931) reported renal lesions in rabbits suffering from neurogenic hypertension progressive hyalinization of the glomerular tufts with atrophy degenerative renal arteriolitis and atrophic lesions in the uriniferous tubules were prominent No one has since confirmed these observations (Kremer Wright & Scarff 1933 Boyd & McCullagh 1938 Hoerner Fontaine & Mandel 1938)

Elaut (1935 1936) reported that neurogenic hypertension was neither prevented nor abolished by denervation of the kidneys Hoerner Fontaine & Mandel (1938) found no evidence of renal failure in dogs with neurogenic hypertension observed for 1½–3 years, their blood urea values were normal and there was no disturbance in phenolsulphone phthalein excretion even after unilateral nephrectomy Alpert & Thomas (1943) determined renal clearance of diodone inulin and urea during periods of low and high protein intake and found no significant difference between normal and neurogenic hyper tensive dogs No significant morbid histological changes were found in the kidneys Bing Thomas & Waples (1945) found however in two out of six neurogenic hypertensive dogs a fall in renal blood flow and glomerular filtration rate As creatinine and *p* amino hippuric acid clearances decreased proportionately while the filtration fraction remained constant they concluded that the afferent renal arterioles were constricted

Bacq Brouha & Heymans (1934) reported that the sino aortic constrictor and dilator reflexes were absent in completely sympathectomized dogs, and that section of both carotid sinus and both aortic nerves in acute experiments was ineffective after total sympathectomy Nowak (1940) however produced moderate hypertension by denerva tion of the vasosensory areas in dogs previously totally sympathectomized In animals with fully established hypertension, subsequent partial sympathectomy including bilateral division of the splanchnic nerves or such operations as unilateral adrenalectomy (cp Kremer Wright & Scarff 1933) bilateral lumbar ganglionectomy or removal of two thirds to three fourths of the thoracico lumbar chain failed to reduce the hyper tension However Schafer (1944) reported that paravertebral sympathectomy lowered the arterial pressure in hypertensive dogs for prolonged periods these animals showed a tendency to develop a second hypertensive phase somewhat less pronounced than before the sympathectomy which was explained by the possible re establishment of some sympathetic functional innervation

Grimson (1940 1941) reported that neurogenic hypertension in dogs persisted after the following operations bilateral renal denervation (cp Elaut 1935), division of the splanchnic nerves and abdominal sympathectomy division of the splanchnic nerves abdominal sympathectomy cœliac ganglionectomy lower thoracic sympathectomy and division of the splanchnic nerves upper thoracic sympathectomy Hypertension of renal origin was produced in dogs after carotid sinus and aortic deafferentation and complete sympathectomy (but for the adrenal and kidney nerve supply) in these animals subsequent denervation of the kidneys considerably reduced the hypertension

Bing Thomas & Waples (1945) investigated the circulatory effects of neurogenic hypertension in unanæsthetized dogs The cardiac output (Fick) in dogs lying quietly was increased by 30–50% while the right intra auricular pressure was normal The arterio venous oxygen difference and oxygen utilization were diminished Limb blood flow was accelerated and the circulation rate was increased The total peripheral resistance rose in only two of six hypertensive dogs The increase in peripheral blood flow was possibly due to active arteriolar dilatation or alternatively to opening the arterio venous shunts They concluded that hypertension was due to the rise in cardiac output as the stroke volume was unchanged the rise in output was ascribed to the increase in heart rate This rise in heart rate amounted in some animals to 85 beats per minute in excess of the pre hyper tensive figures Unfortunately no further studies of cardiac output in animals with

neurogenic hypertension have been made Therefore confirmation of the observations of Bing Thomas & Waples (1945) would be valuable Several points of interest emerge from the work reviewed Denervation of the carotid sinus and aortic vasosensory areas produces hypertension and tachycardia These changes are subject to considerable variations in response to extraneous stimuli and arterial pressures and heart rate may be normal at sleep or complete rest *Failure to produce chronic neurogenic hypertension in* animals is due to incomplete denervation particularly to the presence of baroreceptor fibres in the vagi or to functional regeneration of vasosensory fibres It must further be remembered that baroreceptor areas are located in the pulmonary and mesenteric vascular beds (Schweitzer 1936 Aviado *et al* 1952 Gammon & Bronk 1936 Heymans

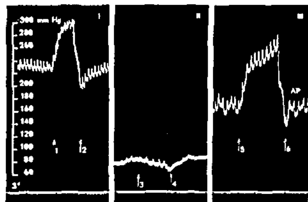


FIG 44 Systemic blood pressure of a dog with chronic renal hypertension (230-240 mm Hg)
1-2 Clamping and unclamping of both common carotid arteries Reflex rise of systemic blood pressure
Between I and II Local carotid sinus application of 0 1 mg noradrenaline Fall of systemic blood pressure from 240 to 80 mm Hg
3-4 Clamping and unclamping of carotid arteries No reflex rise of systemic blood pressure
III After 1 hour 15 min the arterial pressure returned to 170 mm Hg and the carotid sinus pressure reflexes (5-6) re covered —(Matton)

Bouckaert Farber & Hsu 1936 Gruhzit Freyburger & Moe 1954) Although the precise function of these pulmonary and mesenteric baroreceptor mechanisms under physiological conditions is still somewhat obscure it is conceivable that they may modify the effects of carotid sinus and aortic deafferentation In this connection it is of interest that immediately after the denervation of the carotid sinuses and the aorta very high values of arterial pressure and heart rate are recorded these high pressures and tachycardia usually decline after a few minutes and the final result of the operation will not be established before 2-3 weeks (Thomas 1944) The cause of this temporary recovery is unknown and it would be interesting to know whether pulmonary and mesenteric baro *ceptor mechanisms step into the breach to be finally overwhelmed by the full* effects of the absence of carotid sinus and aortic arch restraint of the medullary centres

Neurogenic hypertension presents a very different picture from that of renal hyper tension which is much more stable when fully established However the wide fluctuations of the pressures of animals with neurogenic hypertension resemble the pre hypertensive phase in essential hypertension during which the blood pressure is labile over a wide range of normal and hypertensive levels In experimental renal hypertension and in essential hypertension the cardiac output is held to be normal and hence the total peri pheral resistance is increased Others deny this increase in total peripheral resistance In essential hypertension there is constriction of the renal afferent and efferent arterioles while in neurogenic hypertension only the afferent arterioles if any are involved The rise in

arteriolar pressure in experimental renal hypertension and in essential hypertension is mainly due to the decrease in the arteriolar cross sectional area according to Bing *et al* while they consider that the systemic hypertension after chronic sino aortic denervation may be due to a rise in cardiac output

McCubbin *et al* (1956) showed that the baroreceptors were much less active than might be expected from the level of the mean blood pressure in dogs suffering from chronic renal hypertension As mentioned before it is not clear whether this was due to some form of adaptation on the part of the nerve endings or whether it could be ascribed to structural changes in the arterial wall of the sinus region owing to the effect of the sustained high blood pressure Certainly the animals still showed marked pressor responses to carotid occlusion which indicates that the mechanisms were still functional In this respect it is interesting to note that Matton (1954 1955 1957) has shown that the local application of vasoconstrictor drugs to the wall of the carotid sinuses caused a fall of systemic pressure in renal hypertensive dogs from levels of *circa* 250 mm Hg to a level of less than 80 mm Hg (Fig 44) which suggests that the baroreceptor activity when artificially induced to a maximal extent is as effective as in a normal dog It is possible therefore that changes of distensibility in the sinus wall occur with long standing hypertension which limit the natural cause of excitation of the nerve endings Matton found as did Page and his colleagues that the reflex response to carotid occlusion was well developed in dogs with systemic pressures over 250 mm Hg (Fig 44)

CHAPTER 11

BARORECEPTOR REFLEXES OTHER THAN CIRCULATORY

Sino-aortic Baroreceptor Reflexes Affecting Respiration

Respiratory responses to stimulation of the central end of the aortic depressor nerve were described by many during the 19th century It is of course difficult to be certain whether the depressor nerve was itself stimulated Present knowledge reveals that the baroreceptors exert only an inhibitory effect on respiration However the certain recognition of the aortic nerve in the dog depends on making a satisfactory electro neurographic recording of the nerve selected on laying the nerve on electrodes rhythmic bursts of action potentials should accompany each pulse It is likely that in the absence of such controls nerves other than the aortic were stimulated particularly in the dog thus accounting for the confused reports in the older literature Another difficulty arises from the secondary effects of profound bradycardia and hypotension produced by aortic nerve stimulation Such falls of pressure may cause reflex chemoreceptor stimulation of the breathing Lastly the effects of stimulation of the central end of the vagus nerve should be entirely disregarded Whitteridge has wittily observed that such a procedure should be a punishable offence (1952) and we entirely agree The multiplicity of fibres in the vagi carrying sensory impulses from widely different sites should be considered and then any result might be reasonably expected to ensue from vagal stimulation as is indeed the case

François Franck (1892) observed reflex dyspnœa on stimulating the aortic nerve Knoll (1883) Hunt & Harrington (1897) Tschermak (1866) Scharf (1925) and Jonnesco & Jonescu (1926) however reported apnœa as the result of this experiment

Compression of the carotid area induced variable respiratory reactions (Tschermak 1866 Quincke 1875 Wenckebach & Winterberg 1927 Recht 1924 Danielopolu Aslan Marcu Proca & Manescu 1927)

Both Cooper (1836) and Magendie (1838) observed hyperpnœa as a result of occlusion of the common carotid arteries Kussmaul & Tenner (1855) Rosenthal (1862) Hill (1896) Lumsden (1923) Heymans (1928) Gesell (1928) and Schmidt (1928) showed that a rise of pressure in the carotid-cephalic circulation induced respiratory inhibition which they attributed to a direct central mechanism Pagano (1900) and Siciliano (1900) however had both noted that the hyperpnœa of common carotid occlusion was not seen if the efferent branches of the carotid bifurcation were clamped although the reduction in cerebral blood flow was the same Hering (1927) then showed that the respiratory effects of carotid occlusion were entirely reflex being abolished by section of the sinus nerves Conversely stimulation of the sinus nerve often caused apnœa

Shortly afterwards Heymans & Heymans (1927*a* *b*) proved likewise that a rise of pressure in the aortic arch caused reflex inhibition of the respiratory centre by a vagal pathway (Fig 45)

The electrical stimulation of the sinus nerve (or aortic nerve) may not always cause apnœa owing to the presence in the nerve trunk of chemoreceptor fibres which exert a stimulating effect on respiration Moissejeff (1926) using a rise of static pressure in the sinus was the first to show that apnœa or hypopnœa was the respiratory response to pure baroreceptor stimulation His claims were supported by Heymans (1929*d*) Koch & Mark (1931) Heymans & Bouckaert (1930) Winder (1938) Heymans & Pannier (1946) Marri & Hauss (1939) and Grimson & Shen (1939) (Fig 46)

Euler & Liljestrand (1936 1937 1940) Rudberg (1938) Bjurstedt & Euler (1942) Rudberg (1940) Bjurstedt & Hesser (1942) Gernandt Liljestrand & Zotterman (1945)

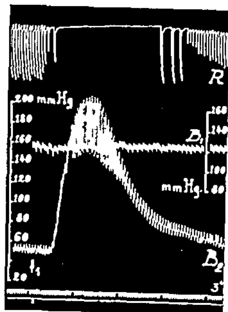


FIG 45 Isolated head of dog B only connected with body of dog B by means of vagi aortic nerves and perfused by dog A (see Fig 9a)
R = respiratory movements of isolated head B
B_1 = arterial pressure of donor dog A
B = arterial pressure of body B
I = intravenous injection of 0 1 mg adrenaline to body of dog B Hypertension in body of dog B and reflex apnœa of head B —(C Heymans)

and Gernandt (1946) have all claimed that respiratory reflexes during carotid occlusion may be due to the reduction of blood flow through the chemoreceptors This mechanism certainly contributes to the hyperpnœa of carotid occlusion and may even contribute to the reflex inhibition caused by a rise of pressure in the so-called isolated carotid sinus preparation Few tie the occipital artery and ascending pharyngeal artery proximal to the origin of the vessels supplying the carotid body Nevertheless if the Gollwitzer Meier ligature 6 (1934) is tied between the carotid sinus and the origin of the occipito ascending pharyngeal trunk from the external carotid artery the internal carotid carotid sinus common carotid artery segment can be subjected to rises of static pressure which reflexly induce hypopnœa although the chemoreceptors are not affected in this preparation It seems most sensible to concede that in ordinary circulatory conditions the baro and chemoreceptors contribute together to the reflex effects of changing systemic pressure on the breathing

Oliver and Schafer (1895) found that the intravenous injection of adrenaline caused apnœa which they wrongly attributed to a direct inhibitory action on the blood pressure

Adrenaline apnœa is however induced by sino aortic reflexes aroused by the rise of pressure which the drug causes If the sino aortic nerves be cut (Heymans & Heymans 1927 Heymans & Bouckaert 1930) or if the rise of pressure be prevented by a compensator (Samson Wright 1930) the drug does not cause apnœa The effect is in any case of only pharmacological interest as the doses required to induce the response are relatively huge Small doses of adrenaline appear to have a direct stimulating effect on the respiratory centre (McDowall 1928 Barcroft *et al* 1956)

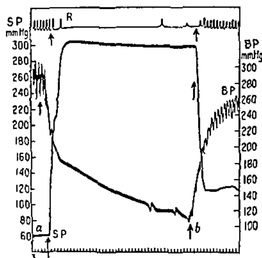


FIG 46 Dog Carotid sinuses isolated and perfused by a pump Records from above downwards show respiration systemic blood pressure sinus perfusion pressure and time in 3 second intervals A rise of sinus perfusion pressure from 60 mm to 300 mm Hg induces reflex systemic hypotension and apnœa —(C Heymans and J J Bouckaert (1930) *J Physiol* 69 254)

Schmidt has several times stated (1940 1941) that the reflex effects of the sino aortic baroreceptors on breathing are probably manifestations of a now useless survival in an air breathing animal of an organization that may have had considerable importance in a water breathing ancestral form On the other hand it is quite clear that a fall of systemic pressure reduces baroreceptor stimulation and thereby increases respiratory activity which is presumably advantageous even to air breathing organisms which suffer blood loss

Baroreceptor Reflex Effects on Bronchomotor Tone

Daly & Schweitzer (1951*a* *b*) investigated the effects of baroreceptor stimulation on bronchomotor tone Since the bronchial musculature is innervated by the vagus nerves it might be expected that reflex changes in bronchial calibre would result from sino aortic reflexes *Bronchomotor effects were measured by recording the tidal air of the animal* under negative pressure ventilation with the chest opened in the mid sternal line Eserine was sometimes given to increase the resting bronchoconstrictor tone The carotid sinus was isolated and perfused A rise of sinus pressure caused bronchoconstriction The authors suggested that the reflex might exist in man thus a rise of systemic blood pressure

produced by general sympathetic activity on receipt of an emotional stimulus might stimulate the sino aortic mechanoreceptors and cause reflex broncho spasm—in spite of the primary effect of adrenaline release (which would cause dilatation of the bronchi) This does not seem very likely Nevertheless Daly & Schweitzer drew attention to the sensation of tightness in the chest experienced by subjects receiving 5–20 µg /min of adrenaline intravenously noted by Henry Barcroft (personal communication) These symptoms appear to be related to the rise of blood pressure caused by the drug and are seen in the initial stages of the infusion Their disappearance can be ascribed to the direct broncho dilator effect of adrenaline which becomes predominant as the drug concentration increases

In a later paper Daly & Schweitzer (1952) showed that bronchodilatation resulted when an animal was subjected to acute hæmorrhage They ascribed this to the reduction of sino aortic impulse activity in the conditions of hypotension They were able to exclude sympathetic effects on the bronchi section of the sympathetic nerves innervating the lungs did not materially affect the bronchomotor response to hæmorrhage They concluded that the sino aortic baroreceptor areas took part in the reflex maintenance of bronchoconstrictor vagal tone in normal conditions

Baroreceptor Reflexes other than Circulatory or Respiratory

The irradiation of autonomic reflexes including those of baroreceptor origin was ably reviewed by Schweitzer (1937) Responses of various systems to baroreceptor stimulation were fully described These included the following —

1 Reflex changes of tone and movement in the gastrointestinal tract Bayliss (1893) observed increased movements and tone of the stomach and small intestine on stimulating the aortic nerve in the rabbit Kisch (1926) confirmed these changes and found in addition that a fall of pressure in the carotid sinus caused conversely gastric atonia and decreased intestinal movement Recht (1924) provoked reflex peristalsis by mechanical stimulation of the carotid sinus in man
2 **Bladder** Koch (1931) showed that an increase of pressure in the isolated innervated carotid sinus caused reflex contraction of detrusor vesicæ
3 **Pupil** Braunstein (1894) claimed that mydriasis occurred in the curarized dog in which both cervical sympathetic trunks were cut on lowering the carotid sinus pressure but mechanical stimulation of the sinus in man caused dilatation of the pupil according to Recht (1924) Hering (1932) and Koch (1932*a* *b*) both observed that sino aortic denervation caused mydriasis
4 **Somatic Reflexes** Tournade & Malmejac (1929) and Koch (1931) found that sinus nerve stimulation or an increase of carotid sinus pressure reflexly lessened muscle tone in anæsthetized animals Similar results were claimed by Schweitzer & Wright (1937*a*) in response to stimulation of the central vagus these authors showed that the knee jerk was inhibited Strychnine convulsions or metrazol convulsions were inhibited by vagus nerve stimulation (1937*c*)

The most dramatic effect of all was produced by Koch (1932) who in a survival dog showed that a rise of pressure in the isolated innervated sinus induced a condition of muscular relaxation similar to sleep (see Figs 35 and 36 in Schweitzer s monograph 1937)

Schweitzer saw this in Koch s laboratory and on coming to England reported it to Samson Wright Wright was incredulous and challenged Schweitzer to reproduce the phenomenon Schweitzer did not succeed but did show that there was an inhibition of muscle tone which they later investigated They injected adrenaline to cause considerable hypertension thus increasing the activity of the baroreceptors and duly caused inhibition of the knee jerk To their surprise however this effect was still seen after sino aortic denervation This in turn led to their studies on the effects of autonomo mimetic drugs on central nervous transmission (1938*a* *b*)

Pinotti & Granata (1954) similarly showed that a rise of carotid sinus pressure depressed the linguo mandibular reflex The same authors (1955) proved that the inhibition of the knee jerk caused by sinus nerve stimulation also occurred in the decerebrate dog without there being any depression in the response of the muscle to direct stimulation They concluded that the reflex pathway of inhibition did not necessarily extend above the metencephalon

Bonvallet Dell & Hiebel (1954) have recently proved that distension of the carotid sinuses within physiological limits causes a progressive reduction in cortical electrical activity as recorded by the electroencephalogram Slow waves appear in the records from the various leads during the maintenance of sinus hypertension on lowering the sinus pressure to zero these fairly quickly give place to the normal fast rhythm The effects are not due to the accompanying changes of blood pressure as might be expected Bonvallet and his co workers proved this by cutting both vagi and transecting the spinal cord in the cervical region as a result sinus distension by raising the pressure from 0–160 mm Hg caused no alteration of the blood pressure but still produced the same changes in the EEG as described above This finding appears to be the first example of an afferent inflow which damps rather than activates the cortex Kreindler (1946) described similar effects earlier—on increasing the pressure in the isolated sinus there was a reduction in cortical activity (recorded by the fronto occipital lead only)—but he did not control whether the alteration in the EEG was simply due to the reflex hypotension Bailey & Bremer (1938) and Zanchetti Wang & Moruzzi (1952) observed no inhibitory effects on the EEG activity during stimulation of the central end of the vagus but made no analysis As Bonvallet and co workers point out the inhibitory effects which might be expected to result from the stimulation of the aortic baroreceptor fibres were probably masked by the accompanying facilitation of the reticular substance by the majority of the afferent vagal fibres

Bonvallet *et al* relate their findings to those of Schweitzer & Wright (1937) Zanchetti Wang & Moruzzi (1952) and Dell (1952) and particularly to those of Koch (1932*a*) who as we have seen showed that baroreceptor discharge reflexly diminished somatic motricity They draw attention to the close proximity—even superposition—of the activating ascending reticular system of Moruzzi & Magoun and the descending reticular formations which cause facilitation or inhibition of the spinal motoneurones Everything points to the baroreceptor afferents exercising their inhibitory effects on the cortex and the somatic musculature via this region of the brain stem

Dell Bonvallet & Hugelin (1954) have also shown that an increase in the blood concentration of adrenaline causes activation of the ascending reticular system in the ponto mesencephalic region This humoral activation of the ascending reticular

tracts causes in turn cortical activation If the brain stem is transected in the pre bulbar region then adrenaline induces particularly vivid cortical activation They ascribe this marked effect to the interruption of the inhibitory ascending reticular pathway from the bulbar region which relays the baroreceptor impulse influx aroused by the systemic *hypertension which the drug engenders The stimulating action of adrenaline on the* reticulo cortical and reticulo spinal systems considerably enhances the level of activity of the whole somatic nervous system A counter regulation is exerted by the baroreceptors of the carotid sinus (and presumably of the aortic arch) acting by way of the inhibitory portion of the bulbar reticulum which moderates the state of neuromuscular activity (See also Dell & Bonvallet 1956*a b* Bonvallet *et al* 1953 Bonvallet Dell & Hugelin 1954)

Gellhorn Yesinick Kessler & Hailman (1942) claimed that changes of the systemic blood pressure (and consequently of sino aortic pressure) altered the reactivity of the somatic nervous system Convulsions could be abolished by mechanical stimulation of the carotid sinus Gellhorn Redgate & Sigg (1953) demonstrated that lowering of the sino aortic pressure induced an increase in cortical excitability Lately Nakao Ballini & Gellhorn (1956) have further investigated these effects The carotid sinuses were exposed and ligatures placed under the sinus nerves Cortical potentials were recorded from various areas Adrenaline and noradrenaline (4 μg/Kg) were injected before and after *sino aortic denervation Adrenaline increased the amplitude of potentials of low* frequency (2–7/sec) before sino aortic denervation but had no effect after the baroreceptor nerves were cut Gellhorn and his colleagues believe that adrenaline causes excitation of the cortex only in relatively large doses With smaller doses adrenaline causes effects which are referable to the systemic hypertension these are (1) an increase in the slow potentials and (2) often a decrease in the fast potentials As sino aortic denervation reverses or abolishes these responses to adrenaline injection they believe that sino aortic inhibitory discharge aroused by systemic hypertension (following the injection of adrenaline) causes the appearance of the slow frequency potentials Their views differ from those of the French workers in that they do not consider that adrenaline exerts any tonic excitatory influence on the ascending reticular system

CHAPTER 12

THE EFFECTS OF ANÆSTHETICS AND OTHER DRUGS ON THE BARORECEPTOR REFLEXES

Induction of Anæsthesia

IT has long been known that the inhalation of ether on chloroform vapour causes bradycardia and hypotension (MacWilliam 1890 Embley 1902 Schafer & Scharlieb 1904 Cattell 1923 Meek 1941) The slowing of the heart however does not occur if the vagi have been cut (Embley 1902) Hering (1927) suggested that the sensitivity of the baroreceptors of the carotid sinus region might be increased from observations made on the effects of mechanical stimulation of the sinus during chloroform anæsthesia Robertson Swan & Whitteridge (1956) have recently confirmed this Cats under chlora lose anæsthesia were allowed to inhale 10–15% ether sporadically The impulse activity in single aortic baroreceptor units in these circumstances was compared with that seen during the inhalation of air by the animal The frequency of discharge of the unit was increased during ether inhalation Similar findings were obtained during the inhalation of chloroform or trichlorethylene vapour in the inspired air in concentrations of 2–4 % In other experiments the right carotid sinus was perfused while activity in a single unit of the sinus nerve was recorded The animal s own blood was used for the perfusion being led from the femoral artery via a reducing valve to the inlet of a pump which perfused the carotid sinus The outflow from the sinus returned via a peripheral resistance to the external jugular vein With this technique the sinus nerve ending was exposed to a constant pulse pressure mean pressure and pulse rate The animal was ventilated by a pump with room air or with air mixtures containing 20% ether During ether inhalation there was an increase in the activity of the nerve endings within one minute from the beginning of exposure

Robertson *et al* (1956) consider that sensitization of the baroreceptors is the principal afferent mechanism responsible for the reflex slowing of the heart observed with chloro form and ether They point out that such a mechanism will also contribute to systemic hypotension but argue that this may be offset by stimulation of the sympathetic centres by the volatile anæsthetics themselves They consider that the effects of sensitization of baroreceptors are most important during the early stages of induction of anæsthesia

Surgical Anæsthesia

If anæsthetization is too deep then there is direct depression of the vasomotor centre As a result the blood pressure falls partly due to a reduction of arteriolar resistance and partly due to reduced venous return consequent upon the loss of sympathetic venomotor tone In such circumstances the baroreceptor impulse activity is itself feeble and the sparse impulse discharge impinges on a depressed centre Naturally the reflex response

to carotid clipping is considerably depressed, for it depends upon a withdrawal of an inhibitory effect on the vasomotor centre Similarly a rise of pressure in the isolated sinus can only exert a minor additional depression of a centre already affected primarily by anæsthetic over dosage

If more normal planes of anæsthesia be employed however then certain general statements can be made as to the anæsthetics of choice for demonstrating brisk sino aortic cardiovascular reflexes (Abe (1936) has shown that these reflexes occur in unanæsthetized rabbits!) Chloralose, cyclopropane Evipan and Pentothal when administered in ordinary anæsthetic doses to dogs do not reduce the cardiovascular responses to sino aortic pressure changes unduly This is easily confirmed by comparing the cardiovascular response to changes of isolated sinus pressure in a decerebrate dog before and after the intravenous injection of the requisite anæsthetic agent The longer acting barbiturates notably barbitone and phenobarbitone profoundly reduce the blood pressure response to sino aortic reflexes and should not be employed in such studies Pentobarbitone is perhaps intermediate in such depressant activity between that of chloralose and barbitone Its use is not incompatible with the demonstration of sino aortic reflexes

Chloralose causes a curious irresponsiveness of the vasomotor centre to baroreceptor stimulation in the cat (Neil Redwood & Schweitzer 1949*a*) This is undoubtedly a species difference and does not occur in dogs and rabbits (Neil *et al* 1949*b* *c*) Chloralose acts particularly in the cat by reducing the response of the centre to the baroreceptor impulses but also reduces the response of the baroreceptors themselves to their natural stimulus On stimulating the central end of the sinus nerve electrically in the cat under chloralose anæsthesia the blood pressure rises This reflex response is due to preponderant effects of the stimulation of the chemoreceptor fibre component (Neil *et al* 1948 1949*a*) Douglas Innes & Kosterlitz (1950) have shown that large doses of pentobarbitone produce similar effects in the cat the vasomotor centre again becoming unresponsive to the inhibitory effects of baroreceptor fibre stimulation though it continues to be excited by the chemoreceptor fibres

In describing the effect of drugs on the baroreceptor reflexes it is suitable to consider the structures involved between the excitation of the sino aortic receptors and the final response on the effector side as measured by a change of blood pressure, (*a*) Intraluminal pressure in the sinus region (*b*) the condition (distensibility tension and deformation) of the sinus wall (*c*) the responsiveness of the nerve endings (*d*) the re ponsiveness of the vasomotor centre to the incoming impulses which may depend on the drive which is exerted on it from other sources (e g higher centres such as hypothalamic and chemical environment as typified by local CO tension) (*e*) the responsiveness of the intermedio lateral horn cells in the thoraco lumbar segments of the cord (*f*) the transmission in the sympathetic ganglion (*g*) the ability of the post ganglionic nerve ending to release the sympathomimetic transmitter and (*h*) the ability of the blood vessels to respond to the sympathetic transmitter

The level of blood pressure is also dependent upon the functional activity of the heart as a pump and on the venous return With this reservation alterations in sino aortic reflexes may be due to effects exerted at any point on this reflex arc some alterations will probably be due to effects produced simultaneously at different parts of the arc

Effects on the Sinus Wall

Drugs which modify the distensibility of the wall or the active tension of the wall will in turn indirectly modify the baroreceptor activity It is unlikely that any drug given systemically exerts any important action of this kind However drugs topically applied to the adventitia of the sinus cause marked effects of this nature as described in another chapter Adrenaline and any other drug which causes vasoconstriction *when applied topically* produces increased impulse activity of the baroreceptors (Heymans & van den Heuvel Heymans 1950) it has been argued elsewhere that such effects may be due to distortion or deformation of the tissue in which the nerve endings lie Topical application of sodium nitrite reduces the baroreceptor impulse activity (Landgren Neil & Zotterman 1952) see Heymans (1953 1955) Heymans *et al* (1951) Delaunois & Martini (1953)

Effects on the Baroreceptor Endings

Local anæsthetics applied topically to the sinus obviously abolish baroreceptor activity —e g procaine papaverine atropine in high concentration (Hering 1927 Hazard *et al* 1953) Similarly local injections of large concentrations of anæsthetics such as ether or chloroform (Landgren *et al* 1953) temporarily abolish receptor discharge as might be expected

Acetylcholine or nicotine injected into the blood or perfusion fluid supplying the carotid sinus causes an increased baroreceptor discharge (Diamond 1955) The mechanism whereby the discharge is evoked is not known but it may concern depolarization of the membrane of the receptor The quantity of acetylcholine required to excite the baro receptors is higher than that necessary to fire the chemo sensory endings but this is most likely due to the relative inaccessibility of the baroreceptors situated as they are in the adven titia provided by a relatively sparse supply of vasa vasorum Acetylcholine or nicotine exci tation of the baroreceptors can be blocked by hexamethonium this does not prevent their response to rises of endo sinus pressure Eserine potentiates the response of the baro receptors to acetylcholine (but not to nicotine) but again does not influence the physio logical response of the nerve ending to changes of sinus pressure These results of Diamond (1955) show clearly that acetylcholine plays no role in the initiation of the response of the baroreceptors to their natural stimulation Moreover it must be remembered that other systemic effects of acetylcholine seen when the drug is given intravenously far outweigh in importance those described in the present context Similarly tetræthylammonium and to a lesser extent hexamethonium which Dontas (1954) claims to excite the baroreceptors exert much more profound pharmacological effects elsewhere in the reflex arc Dontas (1954) who claims that KCl given systemically causes baroreceptor excitation seems unaware that KCl can stimulate the intact nerve trunk

Veratrum alkaloids cause excitation of the sinus nerve endings when injected intra venously (Jarisch & Richter 1939*a b c* Aviado *et al* 1949 Alexander *et al* 1953 Richardson *et al* 1952 Gruhzit *et al* 1953 Rothlin & Cerletti 1954 Jarisch *et al* 1952) Jarisch *et al* found however that veratrine injected intravenously might cause the usual reflex effects of bradycardia hypotension and apnœa in doses which were in sufficient to excite the sinus receptors they ascribed these systemic effects to stimulation of cardiac receptors (see Stutzman *et al* (1951) Swiss & Maison (1952) Maison *et al* (1951)) Veratrine however is a mixture of different alkaloids and it seems more suitable to consider the effects of its constituents when administered separately

Protoveratrine, injected intravenously or into the common carotid artery causes bradycardia and hypotension due essentially to sinus baroreceptor excitation (Martini & Calliauw 1955 Abreu *et al* 1954 Wang *et al* 1954 Fernandez & Cerletti 1955) The hypotensive effect of this drug can thus be produced in the vagotomized dog but is abolished therein on section of the sinus nerves Similar results have been obtained with neogermitrine germitrine and germerine (Wang *et al* 1954) Veratridine however after an initial transient excitatory effect blocks the baroreceptors Andromedotoxin (one of the active principles of Rhododendron maximum) stimulates the baroreceptors (Moran *et al* 1954 *a b*)

According to Ginzel & Kottegoda 5 hydroxytryptamine (serotonin) when injected locally into the carotid sinus circulation stimulates the sinus baroreceptors (1954) Kottegoda & Mott (1955) however found the main reflex effects in the cat to be brady cardia and hypotension produced by the stimulation of afferent cardio pulmonary vagal endings Heymans & van den Heuvel Heymans (1953) claimed that serotonin caused in the dog a respiratory stimulation of mainly central origin

Drugs Effects which Block Transmission of Sinus Impulses to Vasomotor Centre

Ergotamine Samson Wright (1930*a*) made a beautiful study of the effects of small doses of ergotamine on the sino aortic reflexes Rothlin (1923) had previously shown that stimulation of the central end of the aortic nerve did not cause systemic hypotension following the intravenous injection of ergotamine in small doses Wright using doses of 0 1 μg /Kg body weight in the cat found that the carotid sinus vasomotor reflexes were abolished though the dose of ergotamine was insufficient to block the peripheral sympathetic vasomotor nerves Thus the induction of cerebral asphyxia was still accompanied by a marked rise of blood pressure He concluded that ergotamine inhibited the central transmission of the afferent impulses from the baroreceptors Heymans & Regniers (1929) noted that ergotamine might slightly sensitize the sino vagal reflex at the onset of its action but showed also that the drug usually caused eventual suppression of the vasomotor reflexes normally elicitable from the sinus A similar phenomenon occurs in man as noted by Jonnesco & Jonescu (1926) and Nordenfeldt (1941) Heymans Regniers & Bouckaert (1930) concluded that this paralysis of the vasomotor reflexes was due to centrifugal (i e motor) paralysis Thus in a perfused head experiment injection of ergotamine into the cephalic circulation had little effect on the sinus vasomotor reflexes (relayed via the vasomotor centre and the spinal cord to the trunk) Conversely the same injection made into the circulation of the trunk abolished the reflexes There seems some conflict of evidence between the results of Wright and those of Heymans *et al* von Euler & Schmiterlow (1944) showed that ergotamine did not diminish the impulse activity of the sinus baroreceptors or of the chemoreceptors of the glomus The chemo reflexes could be elicited by suitable means and were of normal magnitude whereas the baroreceptor reflexes were abolished These results favour Wright s view that ergotamine blocks the transmission of the baroreceptor impulses at the centre Gernandt & Zotterman (1946) however found that a dose of 0 05 mg/Kg ergo tamine given to a cat caused a reversal of the blood pressure response to asphyxia There was no change in the splanchnic outflow of efferent impulses so their results suggest that some blockage of the peripheral constrictor impulses had occurred

Spinal Anæsthesia

Intermedio lateral Cell Horn

The fall of blood pressure induced by spinal anæsthesia depends on whether a high or a low spinal anæsthetic is administered Sancetta *et al* (1952) who have recently made a detailed study of the hæmodynamic changes induced by spinal anæsthesia refer to the earlier work of Aub (1920) Smith & Porter (1915) and Evans (1928) who made this point clear Herman Morin & Vial (1936) showed that section of the spinal cord from below upwards did not notably lower the blood pressure until the fourth thoracic segment was destroyed Sancetta *et al* (1952) showed that there was an average fall of mean blood pressure of 21% and a fall of cardiac output of 16% in men given a low spinal In a high spinal the blood pressure fell 44% and the cardiac output dropped by 31% In such circumstances the fall in peripheral resistance and the increase in the capacity of the circulation are proportional to the extent of the inactivation of the spinal sympathetic centres by the anæsthetic As the sole pathway of the efferent side of the baroreceptor reflex involving the blood vessels is the sympathetic vasoconstrictor outflow it follows that the baroreceptor vasomotor reflex is suppressed in proportion to the degree of involvement of the spinal centres Heymans Bouckaert & Bert (1932) showed that root anæsthesia by the intradural injection of novocaine or percaine diminished or suppressed the baroreceptor reflexes

Ganglionic Blocking and Stimulating Drugs

The mode of action of the ganglioplegic drugs has been reviewed by Moe & Freyburger (1950) Paton (1954) and Zaimis (1955) All preganglionic fibres release acetylcholine which acts as a synaptic transmitter by depolarizing the ganglion cell and thereby activating it As the mean level of systemic blood pressure is determined by arteriolar tone and cardiac output and as cardiac output in turn depends on the capacity of the venous side of the circulation it follows that the loss of venomotor and arteriolar tone due to interruption of the sympathetic vasoconstrictor impulses by ganglionic blockade will cause a fall of blood pressure The ganglioplegic drugs act as competitive blocking agents at the autonomic ganglia—they do not prevent the release of acetylcholine

The only certain way to test the effect of a given ganglioplegic drug on the baro receptor vasomotor reflex response is to record the change in impulse activity in a post ganglionic sympathetic fibre preparation produced by alterations of pressure in the perfused isolated carotid sinus before and after its administration This has not been done A less satisfactory method of assessing the effects of these drugs has been generally employed Thus the response of the systemic blood pressure to carotid occlusion has been used as an indication of the drug effects This method is not free from reproach The baroreceptor component of the carotid occlusion reflex response depends on the with drawal of the inhibitory effects of tonic impulse activity from the vasomotor centre If the systemic blood pressure is lower than normal then the tonic activity of the sinus nerve endings is correspondingly reduced Any hypotensive drug must reduce the reflex response to carotid occlusion Thus if the threshold mean pressure required to cause demonstrable reflex effects from the sinus on the systemic pressure is 70 mm Hg carotid occlusion at a mean systemic pressure of 70 mm Hg can hardly be expected to produce any reflex response as measured by the blood pressure tracing

The ganglioplegic drugs have unfortunately side actions which influence the effects which they exert on the circulation Moreover any one ganglioplegic is unlikely to be equally effective in blocking all autonomic ganglia Some may be relatively feeble in their power to prevent vagal ganglionic transmission although causing satisfactory blockade of the sympathetic synaptic relay

Moe Rennick Capo & Marshall (1949) showed that TEA infused into dogs at 15 mg /kg /hr abolished the response to carotid occlusion A similar dose also prevented the bradycardia and hypotension caused by stimulation of the sinus nerve The infusion of TEA potentiated the pressor effects of small doses of adrenaline Gruhzit & Moe (1949) showed that Dibutoline in addition to its atropine like action produced effects comparable with those of TEA abolishing the pressor response to carotid occlusion This action was due to ganglionic blockade

Morrison Heymans Richardson & Walker (1951) examined the effects of TEA Parpanit Diparcol and bis (1 trimethylammonium propyl ether) dihydrochloride (MC–2444) on various circulatory responses Among those tested were reflex bradycardia caused by adrenaline the reflex restoration of the blood pressure following tilting the rise of systemic blood pressure caused by carotid occlusion In addition the effect of the drugs in preventing bradycardia during peripheral vagal stimulation was examined TEA had only one fifth of the power of the other three drugs to prevent adrenaline bradycardia However Parpanit and Diparcol were shown to exert a powerful adrenolytic action which naturally limited the rise of pressure caused by injected adrenaline and it was for this reason that they seemed to be more effective than TEA rather than for any ganglioplegic potency TEA and MC–2444 caused striking postural hypotension whereas Diparcol and Parpanit were quite ineffective MC–2444 was nearly four times as powerful as TEA in producing a 50% reduction of the carotid occlusion response whereas Parpanit and Diparcol were respectively one seventh and one third as effective as TEA Conversely TEA and MC–2444 were much less effective than the other drugs in preventing cardiac standstill during peripheral vagal stimulation This was shown to be due to an atropine like action in the case of Parpanit These results re emphasize the need for a complete study of the pharmacological actions of drugs which are ordinarily described as ganglioplegics Halpern du Bouchet & Neveu (1954) showed that the intravenous injection of hexamethonium (0 5–3 mg /kg body weight) markedly depressed the vasopressor reflexes of carotid sinus origin while the hypertensive responses to adrenaline and to the electrical stimulation of the central end of the vagus were considerably enhanced

Adrenergic Blocking Drugs

The pharmacological properties of the adrenergic blocking drugs have been recently reviewed by Bovet & Bovet Nitti (1948) and Nickerson (1949) Injections of adrenolytic doses of these drugs generally block the pressor action of adrenaline or noradrenaline without greatly affecting the response of the blood pressure to carotid occlusion Higher doses of the drugs usually block the vasopressor adrenergic reflexes caused by carotid occlusion without preventing the cardio acceleration which occurs as a reflex response to clamping the carotid arteries (De Vleeschhouwer (1935) Walker Heymans Wilson & Richardson 1950*a* *b*)

CHAPTER 13

VASCULAR RECEPTORS OTHER THAN SINO-AORTIC

Mesenteric Baroreceptor Activity

THE activity of mesenteric baroreceptors was first studied by Gammon & Bronk (1935) Pacinian corpuscles in the cat s mesentery have a close anatomical relationship to the arteries They are found in crotches of arterial branches in the mesenteric root and along the arcade arteries which supply the intestine Recording from the centrally cut splanchnic nerve Gammon & Bronk (1935) noted that the activity in the nerve was related to cardiovascular activity Pulsatile discharges were recorded in a small nerve twig coming from a few corpuscles when the nerve supply to one Pacinian corpuscle after the other was cut the impulses diminished progressively and were finally abolished It was noted that some groups of fibres were active only during systole whereas others fired throughout the cardiac cycle

Perfusion at constant pressure of a portion of the superior mesenteric artery system with Ringer s solution or defibrinated blood caused a continued discharge from Pacinian corpuscles when the perfusion pressure was above a threshold value which varied from experiment to experiment When pulsatile pressure increases were used there was a vigorous burst of impulses Changes in temperature or in the degree of oxygenation of the perfusion fluid did not affect the discharge from the corpuscles

In the intact animal intravenous injection of Ringer s solution (200 ml) greatly increased the afferent discharge the effect persisting for some minutes when 50 ml of blood was withdrawn the discharge decreased or ceased However when a rise in systemic blood pressure was produced by vasoconstrictor drugs e g adrenaline the discharge from the corpuscles decreased whereas acetylcholine or amyl nitrite increased the discharge

The authors concluded that the total sensory discharge from the Pacinian corpuscles was not directly related to the level of the systemic blood pressure but to the degree of distension of the mesenteric vessels as determined by the blood volume This distinguishes the mesenteric baroreceptors from the carotid sinus and aortic baroreceptors which respond to blood pressure changes independent of their mode of production The Pacinian corpuscles have a rich intrinsic blood supply a central vessel pierces their core and a rich network of capillaries is found in the vicinity It is possible that pressure changes within the central vessel may be in part responsible for the excitation of the baroreceptors Adrenaline would then tend to constrict the central arteriole thus decreasing the excitation of the receptor whereas vasodilator substances would increase the afferent discharge

Gammon & Bronk (1935) did not observe significant changes in the systemic arterial pressure when the mesenteric perfusion pressure was altered

Heymans Bouckaert Farber & Hsu (1936) recorded the splenic volume changes in a recipient dog (B) whose spleen was perfused from a donor animal (A) In dog (B) the carotid sinus and aortic nerves were cut A sudden hæmorrhage produced in dog (B) resulted in a constriction of its isolated and perfused spleen, administration of adrenaline pituitrin or ephedrin causing a rise in systemic blood pressure produced a dilatation of the spleen The effects persisted after bilateral vagotomy and high cervical transection of the spinal cord but were abolished by total sympathectomy or by destruction of the

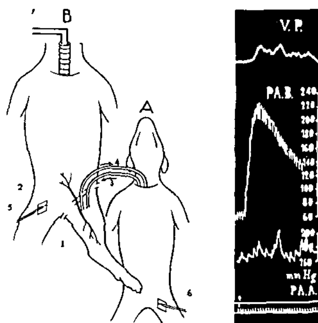


Fig 47 *Left* Isolated body of dog B The isolated but innervated limb of body B is perfused by means of dog A *Right* V P = volume of limb dog B P A B = arterial pressure of body B P A A = arterial pressure of dog A 1 = intravenous injection of adrenaline to body B Rise of arterial pressure in body B induces vasodilatation in perfused limb of body B —(C Heymans J J Bouckaert and M Wierzuchowski (1937) *Arch int Pharmacodyn* 55 233)

spinal cord When a hindleg of a spinal dog (B) was perfused by a donor dog (A) using the Delezenne technique a rise of systemic pressure in dog (B) induced by the injection of adrenaline caused definite vasodilatation of the perfused limb (Heymans Bouckaert & Wierzuchowski 1937) as shown in Fig 47

Heymans Bouckaert & Wierzuchowski (1937) showed in a series of experiments that these baroreceptor reflexes did not originate from the spleen or from the kidney Thus perfusion of these organs at high pressures did not evoke reflex responses in the spinal animal These experimental findings may incidentally be compared with those reported by Dr Agnes Fekete in a discussion held by the Biological Section of the Hungarian Academy of Sciences (1953) following a paper read by Professor Ambrus Abraham Abraham showed in 1943 that there were baroreceptor endings in the wall of the renal artery and referred again to these histological structures in his paper of 1953 Fekete claimed that she had evidence of reflex control of the renal circulation by receptors situated

in arteries below the level of the diaphragm Heymans and his colleagues were able to show that the mesenteric vessels were the site of the nerve endings responsible for the reflexes which they were able to evoke in the spinal dog Thus if an innervated region of the gut with its attached mesentery was perfused by a donor dog (A) a rise of pressure in the mesenteric vessels of dog (B) caused by the injection of adrenaline into the donor animal reflexly induced vasodilatation of the spleen (Fig 48)

The precise function of these mesenteric receptors in the intact organism is as yet unknown It does not appear that they play an important part in the reflex regulation of

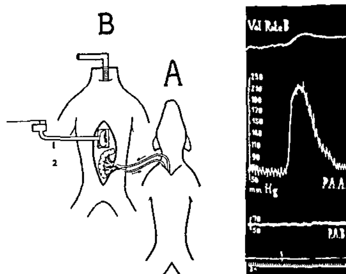


FIG 48 *Left* Body of dog B Isolated but innervated mesenteric intestinal area of body B perfused by means of dog A Registration of volume of spleen of body B *Right* Vol rate B = volume spleen body B P A A = arterial pressure dog A and mesenteric intestinal area body B P A B = arterial pressure body B 1 = intravenous injection of adrenaline to dog A Increase of arterial pressure dog A and intestinal area of body B induces dilatation of spleen body B —(C Heymans J J Bouckaert and M Wierzuchowski (1937) *Arch int Pharmacodyn* 55 233)

systemic pressure Occlusion of the coeliac or mesenteric arteries does not cause a significant change in the blood pressure even of the animal with sino aortic nerves cut (Heymans *et al* 1936) It is likely that these mesenteric receptors are concerned with the local distribution of blood in the abdominal viscera The reflexes which they engender however probably contribute in a minor way to the regulation of cardio vascular activity which is primarily the concern of the sino aortic reflexes

Receptors in the Thoracic Aorta

Gruhzit & Moe (1953) and Gruhzit Freyburger & Moe (1953) have recently shown that baroreceptor reflexes may be initiated from the thoracic aorta Tournade & Malmejac (1933) and Gayet Gayet & Quivy (1933) showed almost simultaneously that an intravenous injection of adrenaline caused vasodilatation in an innervated limb separately perfused

This reflex response was not abolished by sino vagal section Gruhzit *et al* confirmed these findings and even claimed that section of the buffer nerves caused very little difference in the reflex dilatation of the limb evoked by adrenaline They proved that the reflex originated from thoracic receptors Thus in a vagotomized dog whose sinus nerves were cut the injection of adrenaline into either atrium into the pulmonary artery or into either ventricle caused reflex vasodilatation of a degree comparable with that induced by the intravenous injection of the drug Injections made beyond the thoracic arterial vessels were ineffective The response was not that seen in the Bezold Jarisch effect thus the injection of adrenaline into the anterior descending branch of the left coronary artery was no more effective than an intravenous injection moreover cold blocking the vagi when they were intact did not modify the response By denervating the thoracic sympathetic afferents they did not abolish the reflex response and it was necessary to cut all the thoracic dorsal roots before the reflex vasodilatation disappeared By widespread laminectomy they exposed the thoracic dorsal roots from T1 to T12 and by cutting them in groups of three they progressively abolished the reflex response Gruhzit *et al* pointed out that the thoracic aorta is likely to be innervated by sensory nerves of the thoracic segments of the cord The thoracic aorta was cannulated immediately distal to the origin of the left sub clavian artery The aorta was tied above the diaphragm and the arterial segment was perfused by a pump which provided either a mean or a pulsatile pressure Only when the pulsatile pressure was used were reflex responses obtained in an innervated perfused hind limb and these were very feeble compared with those evoked by the injection of adrenaline into the intact animal Gruhzit *et al* concluded that the reflex vasodilatation of the limb induced by adrenaline was initiated by the stimulation of mechanoreceptors in the wall of the thoracic aorta These receptors which are the nerve endings of somatic afferent fibres respond to an increased pulse pressure and not to an increased mean pressure Adrenaline which characteristically causes an increase in the pulse pressure is thus peculiarly well suited to cause discharge of these nerve endings

The importance of these afferent mechanisms in the control of the circulation is not yet clear There have been no electrophysiological studies of these afferent fibres

Peripheral Vascular Receptors

We have argued in previous chapters that the sino aortic baroreceptors play the major role in adjustment of the circulation by nervous mechanisms The recent work on baroreceptor mechanisms in the cardio pulmonary area which is detailed in a later section suggests that these mechanisms play a contributory part It is difficult to determine their quantitative significance owing to the uncertainty which exists at present as to their nervous pathways—as a result it is impossible to denervate these areas selectively Nevertheless we can obtain some evidence of the existence of baroreceptor mechanisms other than sino aortic and cardio pulmonary by studying the vascular response to postural changes in the animal after section of the sinus and vagal nerves

As has been stated the nervous control of venous tone first appreciated by Goltz (1863 1864) in the frog and by Hooker (1918) and Donegan (1921) in the mammal was shown to be under reflex control by Fleisch (1931) Heymans *et al* (1930) and Gollwitzer Meier & Schulte (1931) Jarisch (1928) and Gollwitzer Meier (1932) both concluded that the medullary vasomotor centre under the reflex control of the sino aortic nerves acted

as an integrative centre for both arteriolar and venomotor effects Hess (1930) had already expressed the opinion that the venous system regulated the heart output by changes in the calibre of its constituent vessels and had argued that reflex changes of baroreceptor origin must be important in modifying venous capacity

The assumption of the erect posture tends to reduce the venous return owing to the effect of gravity on the distensible veins Leonard Hill (1895 1896) Hill & Barnard (1897) Hill (1900) clearly appreciated this and was among the first to make any analysis of the compensatory reactions which occurred to offset the effects of gravity on the circulation Hill showed that the compensation for postural changes was best effected in man and the monkey and identified the splanchnic region as the most important source of compensatory vasoconstriction An earlier analysis in man had been made by Schapiro (1881) who measured the heart rate and blood pressure in soldiers who assumed a standing position after lying and found a constant response of tachycardia with a variable response of blood pressure which either remained sensibly constant or rose slightly

Mark & Neumann (1931) pointed out that the reflex effects of manual pressure of the carotid sinus in man were much more marked when the subject lay horizontal than when he stood erect McWilliam (1933) also noted that the heart rate and blood pressure changes evoked by altered posture were not necessarily similar to those which were to be expected as a result of the change of pressure in the carotid sinus and suggested that other reflex mechanisms must be concerned He favoured the existence of sensory receptors in the region of the knee which he supposed were excited in the erect posture Edholm & McDowall (1936) found that the systemic blood pressure might show compensatory changes in anæsthetized cats placed in the erect position even though the sinus nerves and vagi had been put out of action The mesenteric vascular receptors probably contribute to such compensatory reactions Heymans *et al* (1937) showed that a rise in the perfusion pressure of the mesenteric vessels induced a reflex splenic vaso constriction in dogs whose brain had been destroyed and whose sinus nerves and vagi had been cut Destruction of the spinal cord abolished this response There has been with this exception little evidence of reflex mechanisms other than those of the sino aortic zones which might assist in the maintenance of venous return in animals placed in the upright posture As it is generally recognized that the venous return is reduced in the upright position (due to the effects of gravity upon the distensible veins) and as the cardiac output is consequently reduced (Nylin 1934 McMichael 1937) maintenance of the blood pressure or prompt readjustment of the blood pressure to its normal value suggests active vasoconstriction which must include venoconstriction Though the sino aortic regions would appear to be the first and most important defence the results of Edholm & McDowall indicate that other powerful mechanisms can contribute to postural adjustments

Recently interest has been aroused in sensory mechanisms which may lie in the peripheral vasculature Gaskell & Burton (1953) studying the apparent blood flow through the toe using a venous occlusion plethysmograph found that the flow decreased when the leg was lowered below heart level compared with that of a control on the other leg maintained at heart level Conversely when the subject was warm the flow was less in the level position than when the limb was raised at an angle of 15 degrees These findings are the converse of those which might be expected from hæmodynamic principles

and can only be explained in terms of a reflex Moreover as the changes in flow are not parallel to those in the control horizontal limb the reflex effects must be local in character However the same phenomena could be seen in a sympathectomized limb The authors believe that the reflex is evoked by the distension of the walls of the local veins The reflex response of arteriolar constriction is suggested to be mediated via local nerve plexuses in the walls of the vessels As these must be other than sympathetic fibres one would be forced to assume some axon reflex in somatic nerve fibres which seems to operate in a manner opposite to those previously described

Yamada & Burton (1954) have found that the exertion of negative pressure on the finger also reflexly decreases the flow therein, they point out that this finding supports the belief that the sensory receptors are stretch or volume receptors rather than pressoreceptors Haddy & Gilbert (1956) using anæsthetized dogs measured the effect of changes in transmural pressure on the small and large vessel resistance in the foreleg A variable flow pump was interposed in the brachial artery and a needle was inserted in the cephalic vein Retrograde catheterization of a subcutaneous small vein of the paw and a small artery of the foot pad was carried out Pressures at these four sites were measured Maintaining a constant brachial artery flow a tourniquet was progressively tightened on the leg above all the sites of cannulation Cephalic vein pressure was elevated in five steps of 5 mm Hg and after each such rise the various pressures in the remainder of the system were measured After release of the tourniquet the nerves to the lower leg were blocked and the experiment was repeated Pressure gradients were calculated It was found that a rise of cephalic vein pressure of 25 mm was associated with an equal rise of brachial arterial pressure but with a greater rise of the small artery pressure and a smaller rise of small vein pressure While the total pressure gradient therefore did not change there was a decrease in arterial gradient ($-11\ 7 \pm 3\ 8$ mm Hg) a decrease in venous gradient ($-5\ 5 \pm 1\ 5$) and an elevation of the small vessel gradient ($+15\ 5 \pm 4\ 0$ mm Hg) in the innervated limb Hence though the arteries and veins dilated this dilatation was completely compensated in the innervated limb by constriction in the small vessel segment As a result the vascular system did not respond to transmural pressure changes as would be predicted for a simple passive elastic system However after procaine nerve block the vessels did respond like a passive elastic system Therefore the small vessel constriction of the innervated limb must have been of reflex origin involving nervous pathways which extended beyond the leg In further experiments the effect of raising the arterial pressure only (by increasing the flow rate with the perfusion pump) failed to cause reflex constriction of the small vessels The authors concluded that the receptors responsible for small vessel constriction lay in the veins and were excited by an increase in venous pressure (or an increased stretch of the venous walls) The site of the constriction was suggested to be the arterioles Teleological arguments were presented as to the value of such a reflex Thus in the absence of this reflex the flow through a limb would inevitably increase as it was lowered below heart level Reflex peripheral vasoconstriction would thus tend to prevent pooling of blood Haddy & Gilbert (1956) discuss the findings of Gaskell & Burton (1953) and are puzzled by their claim that veno vasomotor effects are still obtained in the sympathectomized limb More evidence seems to be required here

It is interesting to note that congestive heart failure is associated with peripheral vasoconstriction which may be of severe degree thus McMichael (1952) refers to gangrene

of the fingers and nose occurring in such patients Aviado & Schmidt (1955) suggest that the veno vasomotor reflex of Gaskell and Burton provides the explanation of this However they point out that the intense constriction is reduced or relieved by ganglionic blocking agents (Kelley Freis & Higgins 1953, Schuman Lerner & Doane 1954 Burch 1954) or by sympatholytic drugs (Fefjar 1950 Halmagyi Felkai Ivanyi & Hetenyi 1952) It is difficult to harmonize this fact with the statement of Gaskell and Burton that the veno vasomotor reflex persists after sympathectomy The reflex mechanism postulated by Haddy & Gilbert would provide a more probable explanation both of the condition itself and of the effect of sympathicolytic or ganglioplegic agents in alleviating it Venesection (Howard & Leathart 1951) is likewise effective in dispelling the peripheral vasoconstriction and the lowering of central venous pressure which follows digitalization of the failing heart also alleviates the condition (Brigden & Sharpey Schafer 1950 Howarth McMichael & Sharpey Schafer 1946) Brigden & Sharpey Schafer have suggested that the peripheral constriction is caused reflexly by the excitation of cardiac receptors by the raised pressure see also Burch (1956)

Alexander (1956) has found that an acute rise of pressure in the abdominal caval system causes reflex vasodilatation of the intestinal veins which is compatible with the plethora associated with chronic congestive heart failure

Section 2 The Chemoreceptors

CHAPTER 14

HISTOLOGY, EMBRYOLOGY, ANATOMY AND BLOOD SUPPLY OF THE CAROTID AND AORTIC CHEMORECEPTOR AREAS

Historical

THE CAROTID body has been known for a very long time Haller (1743) and (1762) first mentioned the presence of a ganglion in the intercarotid region and Neubauer (1772) also described it according to Sigmund Mayer (1865) Andersch (1777) first gave it the name ganglíolum intercaroticum although Sigmund Mayer states that his work was published many years after he had originally named it thus An anatomist called Mayer is also quoted by Sigmund Mayer as describing the structure independently in 1833 and claiming priority for its discovery although he later (1834) admitted Andersch s precedence see also Valentin (1833)

Lushka (1862) gave the first clear description of the structure noting its rich sympathetic nerve supply in the human subject He described it as glandula intercarotica because his histological examination showed it to be a gland made up of cell columns and vesicles containing only few nerve cells In man the carotid gland was 5–7 mm long 4–2½ mm broad and 1¼ mm thick He also stated that the IXth Xth and XIIth cranial nerves contributed to its nerve supply He considered that the glandula intercarotica was derived from pharyngeal entoderm Svitzer (1863) concurred with Lushka as to the nerve supply Sigmund Mayer (1865) in his dissertation presented at Tubingen before the academic staff (with Lushka in the chair) confirmed Lushka s findings and agreed with him as to the probable embryological derivation of the glandula intercarotica Arnold (1865) was the first to recognize the extraordinary vascularity of the carotid bodies and proposed the name glomeruli arteriosi intercarotici He regarded the glandular tubes and vesicles described by Lushka as ramifying branches of the artery which supplies the body and stated that the epithelial cells found in the structure were those of the lining wall of the blood vessels

Three main theories have been entertained as to the origin and development of the carotid body

1 An origin from the epithelium of the third or fourth branchial cleft (Stieda 1881 Fischelis 1885 De Meuron 1896 Prenant 1894) Szepsenwol (1935) has more recently contributed a study of the first differentiation of the carotid body in embryos of the chick and the duck He stated that the earliest signs of the develop ment of the carotid body occurred from a placode of the fourth branchial cleft ectodermal cells budding off to give rise to numerous polyhedral cells staining well

with silver These cells were already visible in a five day embryo in the middle of a mesh of the pericarotid nerve plexus which together with mesenchymal tissue in the neighbourhood constituted a perivascular swelling in the site occupied by the carotid glomus The main elements of the gland seemed therefore to develop directly from ectoderm from which they emigrated early to concentrate around the fourth branchial arch Although sympathetic cells migrated from the superior cervical ganglion this was at a later stage and such cells did not contribute to the formation of the gland proper

Argaud (1941) stated that en raison de sa structure indeniablement epithelioide et de ses rapports intimes avec les ganglions voisins que son berceau ectodermique se trouve dans une placode tres voisine de la crete ganglionnaire correspondante

2 An origin from the wall of the carotid vessels in the region of the bifurcation (Arnold 1865) This view was upheld by Kastschenko (1887) in studies of pig embryos Marchand (1891) Fusari (1891) Paltauf (1892) Jacoby (1896) Verdun (1898) and more recently by Rabl (1922) Rabl described the first outgrowth of the glomus appearing in the 12 mm embryo as a mass of cells on the ventromedial and ventro lateral sides of the internal carotid artery The cells thus formed were indistinguish able from those of the neighbouring mesoderm which surrounded them

3 An origin from nervous tissue

Schaper (1892) differed fundamentally from earlier authors Die Glandula carotica scheint kein rudimentares Organ zu sein vielmehr durfte ihr in Gemein schaft mit der Glandula coccygea und anderen grosseren oder kleineren Complexen ahnlicher Zellen (Perithelien und Plasma zellen) eine bestimmte physiologische Funktion zukommen deren Specificitat zu ergrunden weiteren Forschungen vorbehalten bleibt He considered the organ to be part of a system widely scattered through the body in relation to the vascular and nervous systems

Stilling (1899) stressed the presence of chromaffine cells in the glomus He did not however regard them as the main cells—only as isolated cells which did not enter into the composition of the lobules His view was that the glomus was a vascular gland similar to the adrenal—a view reminiscent of that of Luschka

Kohn (1900) in a classical paper described the glomus as Paraganglion intercaroticum He summarized his findings (*a*) There is no epithelial formation —this is not a gland (*b*) There are no signs of an organization of perithelial cell or plasma cells—hence this is not a vascular formation (*c*) The structure presents special features and should be placed in the category of organs which lie adjacent to the sympathetic nervous system—the paraganglia (*d*) Its constituent parts—the typical cells the nerve fibres which pass to it and the ganglion cells—resemble the arrangement seen in sympathetic ganglia Das spezifische Gewebselement des Organes ist die chromaffine Zelle

According to Kohn the chromaffine cells in the glomus were derived from the superior cervical sympathetic primordia Smith (1924) also supported this view from the results of studies of embryonic tissue She noted however that in the rat embryo there were no chromaffine cells in the glomus

Histology of the Carotid Body

The modern view of the carotid body stems entirely from the fundamental work of De Castro His account excels not only in giving minute details of the structure but especially in the forecast from his histological findings of the real function of this mysterious tissue De Castro (1926 1928) made three important points



FIG 49 Section of carotid body of adult cat showing the sinusoidal network *a* = artery *a v* = arteriovenous anastomosis *v* = vein Injection preparation (indigo carmine) Magnification 140× reduction to ¾ size —(F De Castro (1951) *Acta physiol scand* 22 14)

1 The nerve supply of the organ is largely afferent and is supplied mainly by the inter carotid or sinus branch of the glossopharyngeal nerve These sensory fibres ramify in most intimate relationship with the epithelioid cells of the body and indeed penetrate these cells to end in their cytoplasm

2 The cells are in close contact with the numerous sinusoids which form a network within the glomus (Fig 49) una complejisma red de vasos sinusoidales con infinidad de anastomosis (De Castro 1940) The cells present one aspect directed towards the sinusoids (pole sanguin) and another which is supplied by the sensory nerves—(pole nerveux) (Fig 50)

3 The so-called chromaffine cells are not true chromaffine cells in that although they reduce potassium bichromate (Henle 1865) this is due to the reducing action of lipoid inclusions in their cytoplasm and is not due to their containing adrenaline like substances Thus he showed that denervation of the gland had no effect on the

intensity of the chromaffine reaction and that insulin shock did not decrease the intensity of the reaction in the innervated gland The cytoplasm contained no adrenaline and he could not obtain any reaction with $FeCl_3$ (Vulpian 1856)

De Castro concluded that the carotid body might sample qualitative changes in the blood De Castro denied that the cervical sympathetic contributed to the innervation of the glomus This might seem surprising in view of the very intimate relationship which sympathetic branches from the superior cervical ganglion bear to the structure but his evidence seems very conclusive The so-called micro ganglions sympathiques which are found in profusion in the walls of the afferent arterioles of the glomus do not degenerate

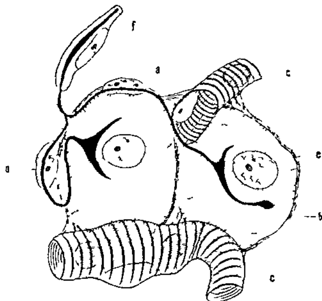


Fig 50 Diagram showing the structure of the synapse in the chemoreceptors The epithelioid cells e present a considerable surface area in close relationship with the blood vessels (c) f = sensory nerve fibre which possesses a myelin sheath a = Schwann cell which encloses the unmyelinated nerve fibres which form the menisques terminaux b = connective tissue network —(F De Castro (1951) *Acta physiol scand* 22 14)

when the corresponding superior cervical ganglion and cervical sympathetic trunk are removed Only when the glossopharyngeal nerve is cut do these nervous structures disappear They are part therefore of a motor pathway from the IXth nerve (and may be important)

Others have remained convinced that the sympathetic contributes to the innervation of the glomus Opinions based on gross dissections (Gerard & Billingsley 1923 Drüner 1925 Hovelacque Maes Binet & Gayet 1930 Cordier & Coulouma 1932 Botar 1932 Delmas & Laux 1933 Ochoterena 1936) are not worth much but those based on embryological evidence (Smith 1924 Benoit 1928 Celestino da Costa 1935 1939 Ito 1950) can hardly be ignored Adams (1955) who cites the above authors makes a good point when he writes When the carotid body was generally considered to be a chromaffine paraganglion (Kohn 1900) the orthosympathetic contribution was almost certainly over estimated whereas now in accordance with the prevailing belief in its chemoreceptor function it is otherwise—the epithelioid cells have come to be associated predominantly or entirely with the glossopharyngeal and to a much lesser extent with the

vagus irrespective of their genetic affinities i e whether they are to be regarded as non chromaffine paraganglionic cells (Watzka 1934 1937 1943) mesodermal cells (Rabl 1922 Boyd 1937) ectodermal cells (Szepsenwol 1935) or modified sensory (ganglionic) cells (Muratori 1933 1934)—there are even some (Goormaghtigh & Pannier 1939) who regard them both as paraganglionic in the conventional sense (i e secretory) and at the same time as nervous (i e sensory)

Even the physiologists remained unconvinced that the sympathetic does not influence or contribute to the function of the glomus Floyd & Neil (1952) found that stimulation of the sympathetic fibres passing to the region of the glomus caused some sensory discharge from the chemoreceptors although this might have been due to constriction of the arteries of supply derived from the occipital artery which is itself very generously innervated by the sympathetic

Boyd (1937) in a major contribution to the embryology of the carotid body studied the development stages in human embryos from 6 mm to 100 mm length A branch of the ninth cranial nerve passes towards the anterior aspect of the third branchial arch artery terminating in the mesodermal cells related to its anteromedial wall (8 mm onwards) A condensation of mesodermal cells supplied by this glossopharyngeal branch appears in embryos of 12 mm situated above the origin of the external carotid on the wall of the internal carotid segment of IIIrd branchial arch artery The lumen of the internal carotid adjacent to this mesodermal condensation becomes flattened and extensions of this deformed lumen are traceable into the mesodermal condensation (20 mm) The meso dermal condensation comprises cells with fusiform nuclei near the endothelium of the internal carotid artery which form the arterial media and adventitia and cells with oval nuclei which later form the carotid body proper The ventral periphery of the condensa tion contains small cells with rich chromatin nuclei derived from the IXth nerve and not from the sympathetic trunk as this is not yet in any close relationship with the third arch artery At 30 mm a separation occurs in the mesodermal condensation loose connective tissue being laid down between the carotid body and the cells which form the adventitia The early blood supply of the body from the internal carotid artery later retrogresses and branches grow from the ascending pharyngeal artery and external carotid artery No sympathetic cells pass to the carotid body until the 30–36 mm stage and hence they form a contribution of secondary importance to a structure derived from mesoderm of the third arch Of the pre neuroblast cells which reach the carotid body from the cranial nerves and sympathetic trunk some form true ganglion cells near the periphery of the organ others retrogress whereas the majority differentiate into isolated cells of the adult carotid body possessing dark nuclei As the main cells occur in whorls these isolated cells can be easily distinguished

Boyd (1937) quotes a rare anomaly in a human cadaver in which the right common carotid artery was absent the internal and external carotid vessels arising from the innominate subclavian arch The carotid body and sinus nerve were absent on the right which can only be explained by an absence of the right third branchial arch and artery

Schumacher (1938) regarded some of the cells of the carotid body as equivalent to the epithelioid elements (Quellzellen) of arterio venous anastomoses This conclusion was contested by Hollinshead (1942) Meijling (1938) made a detailed study of the histological features of the carotid body of the horse He believed that the main cells of

the glomus were of neural origin part of a homogeneous system consisting of interstitia cells of Cajal interstitial plexus and receptor cells The glossopharyngeal fibres reaching the glomus were described as running into a terminal net which surrounded the glomu cells Section of the glossopharyngeal nerve fibres did not cause subsequent degeneration of this terminal plexus which suggests that the relationship of these fibres to the plexu was synaptic The terminal network was described as surrounding on the receptor cells Goormaghtigh & Pannier (1939) also described a terminal plexus unaffected by severance of the glossopharyngeal nerve



Fig 51A Close association of glomus cell type II with vascular supply The direct contact with glomus cells type I is found occasionally (sheep) Holmes s method Fig 51B A glomus cell type II alongside a blood vessel The nervous connections with glomus cells of type I are well seen (rat) Holmes s method —(L L De Kock (1954) *Acta Anat* 21 101)

Hollinshead (1943) denied the neural origin of the glomus cells He described th typical glomus cells as relatively large with a nucleus containing up to three nucleoli Th cell is rounded in shape with well defined boundaries with granular cytoplasm when iro hæmatoxylin Mallory or acid fuchsin are used according to De Kock De Kock (1951 1954) has made some further important contributions to our knowledge of the histolog of the carotid glomus Using a silver method of staining (Holmes 1950) she was able t define five types of cell (*a*) glomus cells type I (*b*) glomus cells type II (*c*) interstitia cells (Cajal 1911) (*d*) pressoreceptor cells (De Castro 1951) (*e*) ganglion cells (Boyd 1937)

In the cat the carotid body is formed by several glomeruli separated by connectiv tissue Each glomerulus contains about 20–30 main cells (type I) and 3–6 type II cells Type II cells are smaller than the main cells and are more ovoid The cytoplasm of type stains blue grey whereas that of type II is pink The nuclei of type I is unstained wherea that of type II is dark red with the Holmes technique Type II cells are characteristicall

interposed between the sinusoids and the type I cells They may be so closely applied to the sinusoid wall as to seem part of it (Fig 51)

Glossopharyngeal fibres having lost their Schwann cell sheath enter the glomerulus and merge imperceptibly into an intraglomerular plexus in which are enmeshed interstitial cells From the interstitial cells fibrils pass to the glomus cells These fibrils pass from one type of glomus cells to the other No evidence was obtained that glossopharyngeal fibres innervate the glomus cells directly On the contrary one or more interstitial cell seemed always to be intercalated between the point of entry of the fibre into the glomerulus and the glomus cells themselves (see also Abraham 1942) This finding of De Kock contradicts the statement of De Castro (1944) that the glossopharyngeal fibres pass directly to the chemoreceptor cells where they end in a menisque d aspect lamelliforme According to de Castro (1951) after section of the IXth nerve the fibres and menisci degenerate De Kock states that the meniscus of De Castro is probably produced by overstaining of the delicately granulated nerve fibrils which reticulate within the cytoplasm of type I cells as she was able to show and which was first demonstrated by Meijling with methylene blue preparations Her results are in substantial agreement with those of Meijling with regard to the relationship of interstitial and glomus cells but she is justifiably much more cautious than Meijling who ascribed a neural origin to the glomus cells type I As she says the close association of the glomus and interstitial cells proves nothing about the neural origin of the former for a similarly close association exists in the frog intestine (Leeuwe 1937) between interstitial cells and smooth muscle cells of the circular layer In addition although she does not make the point Boyd s results would seem to exclude once and for all any neural origin of the glomus cells

The Aortic Bodies

Wiesel (1906) described in a morphological examination of the heart in children a cylindrical mass of greyish pink tissue embedded in the epicardial fat around the left coronary artery as it ran medially to and behind the left atrium On histology it was found to consist of chromaffine cells Trinci (1909 1912) observed similar chromaffine tissue which he labelled cardiac paraganglia at the base of the heart in reptiles and mammals Busachi (1912) in two fully developed embryos distinguished two isolated groups of paraganglia an upper group immediately under the concavity of the aortic arch and a lower group near the left coronary artery as described by Wiesel (1906) According to this author the lower group could not be found in the adult The upper group of cells was not chromaffine Watzka (1930) and Penitschka (1931) further contributed to the study of the cardiac paraganglia in man and mammals Penitschka confirmed Busachi s contention that the upper paraganglia were non-chromaffine He noted the similarity of the histological structure to that of the carotid body and stressed the rich innervation by vagal and sympathetic nerves He gave it the name *paraganglion aorticum supracardiale* defining its position as being between the aortic and pulmonary arteries extending from beneath the concavity of the arch up to the ligamentum Botalli Palme (1934) confirmed Busachi s observation that there were two groups of paraganglia and labelled them *paraganglia supracardiale superius et inferius* The upper group was non chromaffine and the lower group was mainly chromaffine The upper group in new born cats or human embryos was occasionally supplied by a branch of the pulmonary artery

Seto (1935) who like Palme gave full histological details of an examination of the aortic paraganglia in adult human beings described the situation of these as between the aorta and pulmonary artery (see Fig 52) The innervation was found to be parasympathetic and he concluded that the afferent impulses from these paraganglia were conducted in the aortic nerves The arterioles of the paraganglia were shown to contain a wealth of baroreceptor endings presumably derived from the aortic nerve

Muratori (1935) was the first to describe in mammals two paraganglia situated in the angle of the left subclavian and the brachiocephalic on the left and in the subclavian

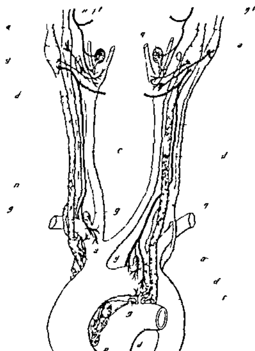


FIG 52 Diagram showing the innervation of the carotid and aortic zones *n g f* = glossopharyngeal nerve *n int c* = sinus nerve *s c* = carotid sinus *g c* = carotid body *a o* = occipital artery *g n* = nodose ganglion *g c s* = superior cervical ganglion *d d* = aortic nerves *n v* = vagus *n s* = sympathetic trunk *g c i* = inferior cervical ganglion *r r* = recurrent laryngeal nerves *a* = ansa of Vieussen *dr dr* = vagal branches to aortic arch *a i* = brachiocephalic artery *c* = common carotid artery *p a* = paraganglion of Penitschka *g* = aortic body —(F De Castro (1951) *Acta physiol scand* 22 14)

carotid angle on the right respectively He found these to be non chromaffine and showed that they were generously innervated by sensory nerves Nonidez (1935) confirmed both the situation and the innervation of these structures in cats and rabbits and described the blood supply as being usually from the subclavian or the brachiocephalic artery Nonidez also later confirmed Palme s description of a pulmonary supply of the paraganglion aorticum supracardiale in the kitten and claimed that the structure was supplied by mixed venous blood He suggested the name glomus pulmonalis However Goormaghtigh & Pannier (1939) showed that this pulmonary supply though present in the fœtus was obliterated in the adult cat being replaced by an arterial supply derived from the coronary artery Nonidez (1935) referred to species differences of the localization of the paraganglia in dogs rabbits and cats He described paraganglionic tissue between the aortic arch and the pulmonary trunk as the aortic body its site corresponding to the structure described as *paraganglion aorticum supracardiale* in man by Penitschka Its blood supply arose from the dorsal surface or concavity of the aortic arch Tissue

corresponding to the *paraganglion supracardiale inferius* of Palme was found lying between the ascending aorta and the pulmonary trunk receiving its blood supply from the left coronary artery Boyd (1937) found four structures roughly corresponding in position to the glomi aortici of Nonidez and the superior and inferior paraganglia in the human fœtus From the 13 mm stage onwards the vagi and sympathetic contributed to these formations and in his view the term paraganglion seemed more valid applied to these structures than to the carotid body In later stages however the histological appearance became progressively more similar to that of the carotid body He considered it probable that the aortic body was derived from the fourth left branchial arch artery and vagus nerve but pointed out that the relationships were not as clear as in the third arch (See Hammond 1941 Tschernjachiwsky 1929 1938)

Goormaghtigh & Pannier (1939) extended their previous studies on the cardio aortic paraganglia and described the situation and blood supply in the cat in considerable detail These authors first drew attention to the numerous arterio venous anastomoses in the supracardiac ganglion (=aortic body) The innervation was stated to be by fibres of the aortic nerve

Comroe (1939) by retrograde intra aortic injections of lobeline or cyanide demonstrated that chemoreceptor zones lay adjacent to the concavity of the aortic arch in dogs supplied by a small vessel which left the aorta opposite the origin of the brachiocephalic (Addison & Comroe 1937 1938) He was unable to evoke chemoreceptor reflexes by injection of such excitants in the region of the pulmonary bifurcation Gernandt (1946) repeated Comroe s experiments in cats and demonstrated that activation of the aortic body by intra ventricular cyanide or lobeline evoked action potentials in the aortic nerves which were similarly aroused by anoxia or hypercarbia In the rabbit no chemoreceptor fibres were found in the aortic nerves Neil Redwood & Schweitzer (1949*c*) using Comroe s technique in cats claimed that the chemoreceptor pathways were via the aortic nerves and the vagi on each side but mainly on the right Similar studies were carried out in the monkey and the dog by Verdonk (1941)

Anatomy and Blood Supply of the Aortic Bodies

Howe (1956) has recently made a careful study of the position and blood supply of the aortic bodies in the cat The vasculature was demonstrated by the injection of coloured masses of Hycar latex or gelatin Indian ink and rice starch The location of the groups of glomus tissue was very similar to that shown in the accompanying figure (Fig 52) Four main groups were shown

Group 1 On the ventral surface of the root of the right subclavian artery

Group 2 On the ventral surface of the root of the left subclavian artery

Group 3 On the ventral surface of the aortic arch superior to the ductus arteriosus and inferior to group 2

Group 4 In the connective tissue deep between the aortic arch and the pulmonary arterial trunk

Group 1 was located in three of nine animals examined Its arterial supply was a small vessel which arose from the root of the right subclavian artery in the angle formed by this vessel with the right common carotid artery The venous drainage which was

derived from a plexus of fine vessels emerging from the glomus ran rostrally as a small vein along the ventral surface of the right subclavian artery to enter the dorsomedial aspect of the superior vena cava at the level of the left costo cervical vein

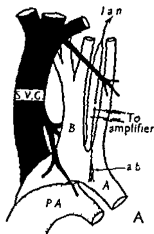
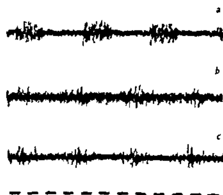


FIG 53 A composite figure from illustrations of Diamond and Howe's paper (1956) (*J Physiol* 134 319)
A Shows recording electrodes on branch of aortic nerve arising from chemoreceptor structure on ventral surface of aortic arch Aortic arch and its daughter vessels are shown plain Pulmonary trunk stippled and superior vena cava and its tributaries black
B Paraffin section of an aortic body (Group III) together with its small artery of supply (on left) Hæmatoxylin and Orange E—erythrosin 8μ thick
C Activity in aortic chemoreceptor nerve during (*a*) breathing air (B P 120 mm Hg) (*b*) breathing 5 per cent O_2 in N_2 (B P = 120 mm Hg) (*c*) air breathing ½ min later (B P = 112 mm Hg) Time in $\frac{1}{10}$ second





Group 2 present in four of nine animals was supplied by a small arterial branch arising from the dorsal surface of the root of the left subclavian artery its venous drainage was by two or three small veins which joined a tributary of the superior vena cava or a branch of the left costo cervical vein

Group 3 were present in seven of nine cats and usually comprised one to four separate small groups scattered along the terminal part of the left depressor nerve The arterial supply was from the dorsal surface of the brachiocephalic artery the arterial branch ran behind the aorta and emerged on the ventral surface of the aortic arch having looped round the ductus arteriosus The venous drainage joined a tributary of the superior vena cava or a branch of the left costo cervical vein

Group 4 was the most difficult to locate lying deeply in the connective tissue between the ascending aorta and the pulmonary trunk The arterial supply was derived from the right coronary artery Diamond & Howe (1956) are the first to record impulse activity from a nerve which was anatomically proved to originate from an aortic body The accompanying figure shows the site of the chemoreceptor tissue and the position of the electrodes on the left aortic nerve which supplied it (Fig 53a) Fig 53b shows the typical histology of the chemoreceptor tissue and Fig 53c displays the electroneurographic evidence of chemoreceptor activity during anoxia In confirmation of earlier work of Bogue & Stella (1935) and Landgren & Neil (1951) they found that hæmorrhage caused an increased discharge of impulses from the chemoreceptors

Anatomy and Blood Supply of the Carotid Body

The carotid body in the common laboratory animals is situated on the root of the occipital artery or on the common trunk of the occipital and ascending pharyngeal arteries a few millimetres rostral to the carotid bifurcation The carotid body (or glomus) is a reddish structure which can be seen with the naked eye although the actual bulk of chemoreceptor tissue is much smaller than it appears This is due to the sinus nerve fibres which course over and round the structure Chungcharoen *et al* (1952*a*) describe the structure in the rabbit cat and dog as having the following dimensions respectively rabbit 1 3×0 75 mm cat 1 4×0 8 mm dog 2 22×1 6 mm Adams (1955) reasonably criticizes these measurements as being perhaps too generous as no histology was done and as the vessels were injected under pressure Adams indeed draws attention to the danger of mistaking parathyroid III for the carotid body in many species Thus Choudhary (1950) mistook parathyroid III for the carotid body in the lizard *Varanus monitor* and Ask Upmark (1935) who claimed that the carotid body of the marsupial *Didelphis virginiana* was very large made this same mistake Adams (1952) proved that the structure in the lizard *Varanus varius* which lies at the bifurcation was parathyroid III and showed that the carotid body in the adult marsupial *Trichosurus vulpecula* was only about 1 mm long as might be expected

In the cat dog and rabbit however there is no doubt as to the identity of the glomus tissue which is innervated by the sinus nerve which runs on to it and even ensheathes it on its way to the carotid sinus

Schaper (1892) and Goormaghtigh & Pannier (1939) both described the blood supply in the cat as being from several arteries which originated from neighbouring vessels in the vicinity of the carotid bifurcation Davis & Story (1943) whose paper on the cerebral circulation of the cat deserves to be widely known described the carotid body blood supply as being derived from the common trunk which gave origin to the occipital and ascending pharyngeal arteries Winder (1933) referred to the glomus blood supply

in the dog as distressingly variable involving many fine vessels Comroe & Schmidt (1938) stated that the blood supply was from *one* small artery which arose from the occipital or the extended carotid This small artery often continued to supply other tissues in the neck anastomosing freely with branches of the pharyngeal and vertebral arteries They believed that the artery served both as afferent and efferent vessels to the carotid body because Addison & Comroe (1937) had seen that the artery supplying the carotid body lost most of its muscular coat and assumed a vein like appearance near the carotid body attachment No venous channels were found This description is peculiar to these authors and was later repeated by Schmidt & Comroe (1940)

*Chungcharoen (1952) and Chungcharoen Daly & Schweitzer (1952) have lately in*vestigated the problem seriously by injecting the structures in the region of the bifurcation with hycar latex or Indian ink Their results may be regarded as the most complete contribution to this subject and may be conveniently summarized

Cat The carotid body lies usually on the occipito ascending pharyngeal trunk or occasionally on the occipital artery itself Two arterial branches which arise from the vessel to which it is attached supply the body A fine venous plexus originating from the body drained into veins which join the internal jugular vein

The authors mention that the veins may join the external jugular vein This is true but the direction of venous drainage of the carotid body is invariably medially towards the internal jugular vein It is very common for venous tributaries of the neck to make connections with both the external jugular and with the venous drainage of the carotid body but direct examination with the aid of the microscope always shows blood from these anastomosing veins flowing towards the body and then onwards medially to the internal jugular vein

Dog Most commonly the carotid body lies on the proximal part of the occipital artery sometimes it is found on the ascending pharyngeal artery The body is supplied by three or four arteries which originate from the artery to which the glomus is attached There is however considerable variability even in the same animal on comparing both sides The venous drainage is again into the internal jugular

Rabbit *The carotid body may be either on the dorso medial aspect of the internal* carotid artery or on small un named branches of the external carotid which arise close to the bifurcation The arterial supply is derived from one or two small arteries which have their origin from the external or internal carotid or from the carotid bifurcation region itself The venous drainage is into the internal jugular vein (See also Addison 1945)

Local Control of the Glomus Circulation

Although the extraordinary vascularity of the carotid body was referred to by Lushka Mayer Arnold Schaper & De Castro it was only in 1939 that Goormaghtigh & Pannier noted the arteriovenous anastomoses which characterizes glomus tissue Actually Schumacher had described the glomus coccygeum in the human subject as being essentially a mass of arterio venous anastomoses and had pointed out that the epithelioid cells seemed to be transformations of the smooth muscle fibres of the middle coat of the arteries Schumacher in 1938 later pointed out that the Quellzellen of arteriovenous

anastomoses were very similar to the epithelioid cells of glomus tissue and although Hollinshead (1942) did not agree Schumacher would seem to have been quite right De Boissezon (1943 1944) De Castro (1940) and Celestino da Costa (1944) confirmed the presence of numerous a v anastomoses in the carotid glomus tissue

The arteries of supply of the carotid body divide into numerous arterioles from which at the surface of the organ these a v anastomoses take origin De Castro (1926 1928

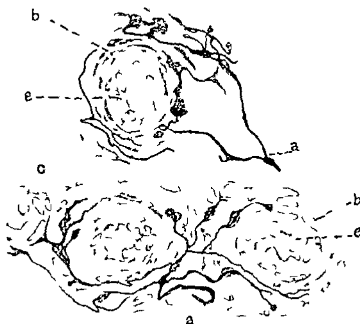


FIG 54 Baroreceptor innervation in the arterial segment communicating with two arterio-venous anastomoses a = nerve fibres with endings in the adventitia e = intima b = media Carotid body of adult cat Cajal method Magnification 1100× reduction to ½ —(F De Castro (1926) *Trav lab Invest biol Univ Madrid* 24 365)

1940 1951) drew attention to the dense baroreceptor innervation of the glomeric arterioles (Fig 54) These endings are similar in function to those of the sinus proper and indeed stimulation of the root of the vessels supplying the glomus initiates reflex hypotension (de Castro 1940) Other cells found in the adventitial wall of the arterioles of the glomus though labelled microganglions sympathiques do not degenerate following section of the cervical sympathetic trunk and disappear only when the sinus nerve is cut This efferent system of the sinus nerve might serve a vasomotor function but this is unknown It is possible that activity in these efferent fibres might be engendered or reflexly modified by baroreceptor impulses which arrive at the glossopharyngeal motor nucleus from the afferent vessels of the glomus but the recent experiments of De Castro (1951) do not

support this Thus De Castro examined the local circulation of the glomus under a magnification of a hundred times In cats breathing normally the venous blood flow was moderately slow and the carotid body size could be measured Changes of chemical composition of the arterial blood such as hypercapnia or hypoxia altered the local circulation the glomus diminished in size the capillary circulation was reduced and the venous outflow became brisk He inferred that arterio venous anastomoses had opened up through which blood flowed more readily at the expense of the glomus capillary circulation Conversely during hyperventilation with pure oxygen the carotid body became larger and the venous outflow became sluggish It seemed as if chemoreceptor activity was associated with increased patency of the a v anastomoses Changes of systemic blood pressure produced mechanically did not alter the appearance of the local circulation from that during eupnœa This does not support any belief in there being any reflex alterations of the glomus circulation caused by changes of activity in the baroreceptors of the afferent arterioles of the carotid body

He described however without further comment the effect of adrenaline given intravenously (0 20 mg) in producing not only systemic hypertension but also an increase in size of the glomus with slowing of the circulation It is possible that the large blood concentration of adrenaline caused contraction of the muscle elements of the wall of the a v segment This invites the speculation whether the a v shunts are themselves controlled by sympathetic fibres which freely supply the afferent vessels of the glomus If this be so then chemoreceptor activity may modify the local circulation by reflexly exciting sympathetic centres This however is mere hypothesis for nothing is known of the innervation of the a v shunts in this region Nevertheless the problem is one of great importance for the electroneurographic technique of assessing chemoreceptor activity entails section of the sinus nerve near its junction with the glossopharyngeal from this length of nerve attached to the carotid body suitably fine strips are dissected and tested for chemoreceptor activity Hence if there is any reflex nervous regulation of the arterio venous shunts by chemoreceptor activity this mechanism has already been destroyed The only exception to this statement would be a nervous regulation of the patency of the a v shunts engendered by chemoreceptor activity and effected by means of an axon reflex such a mechanism would be undisturbed by the above procedure One further possibility exists that the anærobic metabolites produced in the chemoreceptor cells may diffuse to the region of the a v shunts producing vasodilatation by direct chemical influences As the site of the shunts is well upstream (loin de l endroit ou l artere se ramifie pour modeler le glomerule capillaire sinusoidale) this does not seem very likely It is important to control this point by endeavouring to dissect off a fine chemoreceptor branch from the sinus nerve without destroying the continuity of the nerve as a whole The impulse activity in this branch aroused by suitable chemical stimulation can then be registered before and after section of the sinus nerve trunk

Measurement of the Blood Flow through the Carotid Body

M de Burgh Daly Lambertsen & Schweitzer (1954) measured the blood flow and oxygen usage of the carotid body in the cat In view of the important implications of their results the technique employed must be described in detail

The carotid bifurcation area was exposed and dissected free from neighbouring structures except for its venous connections and for those with the nodose ganglion and superior cervical ganglion The cervical vagosympathetic nerve was cut between ligatures about 2 mm caudal to the nodose ganglion to exclude blood from the superior thyroid artery The internal jugular vein was identified for subsequent cannulation All arterial branches of the common and external carotids were tied All veins entering the region were tied except that which was used for cannulation A loose ligature was put round the internal jugular vein and the ninth tenth and eleventh cranial nerves collectively as they emerged from the skull In some experiments the glossopharyngeal and sinus nerves were preserved so that reflex responses from the perfused carotid body could be tested The animal was given heparin to render the blood incoagulable A cannula was tied in the internal jugular vein and the mass ligature was then tightened A glass tube of 0 5 mm bore graduated in 1 cm lengths was connected directly to the cannula and held horizontally by clamps at a level about 1 cm below that of the carotid sinus The flow was measured by timing the advancing column of blood over a distance of 10–20 cm

Table I
(De Burgh Daly, Lambertsen & Schweitzer 1954)

	Before ganglionectomy		After ganglionectomy	
	B P (mm Hg)	Blood flow mm /min	B P (mm Hg)	Blood flow mm /min
	125	70	140	50
	145	78	150	55
	150	79	130	25
	145	120	135	47
	120	80	120	29
	105	62	105	22
Mean	132	82	130	38

Sedimentation of blood was largely avoided by maintaining external carotid blood flow Blood oxygen content of arterial and venous samples was measured by the micro gasimetric technique of Roughton & Scholander Elaborate precautions were taken against contamination with blood from sources other than the carotid body

In thirteen experiments in which the combined blood flow through the carotid body superior cervical and nodose ganglia was measured the average value obtained was 63 mm ^{3}/min (range 11–120 mm ^{3}) In six of these experiments the change in blood flow was determined following the extirpation of the superior cervical and nodose ganglia The results (given in Table I) presumably express the magnitude of blood flow from the carotid body itself

De Burgh Daly and co workers showed that a reduction of the mean systemic blood pressure lowered the blood flow The flow fell to zero when the blood pressure fell to 40–50 mm Hg Since the cervical vago sympathetic trunk was cut the participation of nervous effects was ruled out Conversely 25 μg of adrenaline given intravenously caused the usual rise of blood pressure and increased the carotid body blood flow

Stimulation of the cervical sympathetic trunk caused a reduction in blood flow through the carotid body Since all nerves leaving the superior cervical ganglion other

than that supplying the region of the carotid bifurcation and the glomus were cut this effect must have been due to vasoconstriction

Measurement of the oxygen content of arterial and Carotid body venous blood revealed that there was no significant arteriovenous oxygen difference across the carotid body providing that the carotid body blood flow was normal (i e c 40 mm ^{3}/min) The blood pressure was therefore lowered until a steady flow of about 10 mm ^{3}/minute was reached Measurements of oxygen content then revealed that there was a significant arterio venous difference of about 2 0 ml /100 ml

As the authors point out the significance of a value for the carotid body blood flow cannot be fully appreciated until it is expressed in the conventional manner of ml blood/ 100 g tissue/min It was found on the basis of eleven observations that the average weight of the carotid body is 1 8 mg (range 1 3–2 25 mg) Thus a flow of 40 mm ^{3}/min for a 2 mg carotid body is equivalent to 2 000 ml /100 g of carotid body tissue/min This clearly shows the glomus to be much the most vascular tissue in the body De Burgh Daly *et al* compare these figures with those of brain (60 ml /100 g /min Dumke & Schmidt 1943) and heart (64–151 ml /100 g left ventricle/min Gregg 1950) To these figures we may add that usually given for the thyroid gland—560 ml /100 g /min

Considering the possibility of arteriovenous shunts (Goormaghtigh & Pannier 1939 De Castro 1940 1951) they argue that De Castro presented evidence which suggested that only a small proportion of the carotid body blood flows through the a v anastomoses when the chemoreceptors are quiescent Their contentions here are not entirely sound—de Castro made his observations on innervated carotid bodies whereas De Burgh Daly *et al* studied the denervated carotid body As it seems likely that the a v shunt mechanism is under nervous influences it is perhaps dangerous to ignore this If the a v shunts of the denervated body were patent these high rates of blood flow would mean little However the authors score a further point when discussing the metabolism of the carotid body With the observed average reduced blood flow of 9 mm ^{3}/min and an arteriovenous difference of 2 0 ml /100 ml the oxygen usage is 0 00018 ml O_2/min As the average weight of a carotid body was 2 mg the carotid body oxygen consumption is 9 ml /min /100 g tissue or nearly three times that found by Kety & Schmidt (1945) for the rate of cerebral oxygen uptake Now if the blood flow measured is occurring partly through shunts then the greater the shunt flow the higher must be the oxygen usage of the carotid body tissue Moreover bearing in mind that the glomus tissue is virtually interlaced by vascular sinusoids composed of tissue with a very low O_2 consumption then it is likely that the epithelioid cells have a very active metabolism indeed

These fundamental studies have entirely changed our outlook on the oxygen needs of the carotid body Comroe & Schmidt (1938) showed that when blood equilibrated *with carbon monoxide was perfused through the carotid body a reflex* hyperpnœa resulted This ceased as soon as oxygen was bubbled through the blood although its oxygen content was increased by only 0 42 ml /100 ml most of which presumably went into physical solution They concluded that these receptors are satisfied with a small amount of oxygen provided that the tension remains normal and that the amounts of oxygen carried in simple solution in the blood evidently are more than adequate to meet the needs of the small mass of tissue but the tension of the gas must be maintained nearly at a normal level for this to occur De Burgh Daly and co workers however have shown

The carotid bifurcation area was exposed and dissected free from neighbouring structures except for its venous connections and for those with the nodose ganglion and superior cervical ganglion The cervical vagosympathetic nerve was cut between ligatures about 2 mm caudal to the nodose ganglion to exclude blood from the superior thyroid artery The internal jugular vein was identified for subsequent cannulation All arterial branches of the common and external carotids were tied All veins entering the region were tied except that which was used for cannulation A loose ligature was put round the internal jugular vein and the ninth tenth and eleventh cranial nerves collectively as they emerged from the skull In some experiments the glossopharyngeal and sinus nerves were preserved so that reflex responses from the perfused carotid body could be tested The animal was given heparin to render the blood incoaguable A cannula was tied in the internal jugular vein and the mass ligature was then tightened A glass tube of 0 5 mm bore graduated in 1 cm lengths was connected directly to the cannula and held horizontally by clamps at a level about 1 cm below that of the carotid sinus The flow was measured by timing the advancing column of blood over a distance of 10–20 cm

Table I
(De Burgh Daly Lambertsen & Schweitzer 1954)

	Before ganglionectomy		After ganglionectomy	
	B P (mm Hg)	Blood flow mm /min	B P (mm Hg)	Blood flow mm /min
	125	70	140	50
	145	78	150	55
	150	79	130	25
	145	120	135	47
	120	80	120	29
	105	62	105	22
Mean	132	82	130	38

Sedimentation of blood was largely avoided by maintaining external carotid blood flow Blood oxygen content of arterial and venous samples was measured by the micro gasimetric technique of Roughton & Scholander Elaborate precautions were taken against contamination with blood from sources other than the carotid body

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Stimulation of the cervical sympathetic trunk caused a reduction in blood flow through the carotid body Since all nerves leaving the superior cervical ganglion other

Chapter 15

THE CHEMORECEPTOR REFLEXES AND THE RESULTS OF ELECTROPHYSIOLOGICAL STUDIES OF THE CHEMORECEPTORS

Aortic Chemoreflexes

J F & C Heymans discovered the first of the peripheral chemoreceptor reflexogenic zones in 1927 A donor dog (A) was used to perfuse the head of a recipient (B) The head of (B) was connected to its trunk solely by the vagi The trunk was artificially ventilated Movements of the alae nasi or the larynx were recorded graphically in order to sample

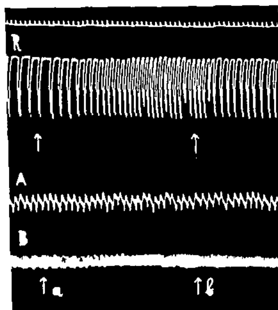


Fig 55 R = respiratory movements of isolated head of dog B perfused by means of a dog A Vagi aortic nerves alone connecting head B to body B The lungs of body B are denervated A = arterial pressure of dog A B = arterial pressure of body dog B a b = asphyxia of body B induces reflex stimulation of respiratory centre of head B —(J F and C Heymans (1927) *Arch int Pharmacodyn* 33 272)

activity of the respiratory centre of the head of (B) The arrangement was as shown in Fig 9

Asphyxia anoxia or hypercarbia of the trunk caused increased activity of the respiratory centre of dog B as shown by increased movements of the alae nasi (Fig 55) Conversely hyperventilation of the trunk abolished activity of the respiratory centre These effects were abolished by vagotomy In further experiments Heymans & Heymans proved that the cardio aortic area was the site of the chemoreceptors Three dogs A B and C were used and the isolated head of (B) was supplied by the donor (A) In the trunk of (B) (connected to its respective head by the vagi) the azygos vein the internal

mammary left subclavian and right vertebral arteries were tied and the aortic arch was ligated distal to the origin of the left subclavian artery The inferior vena cava was also

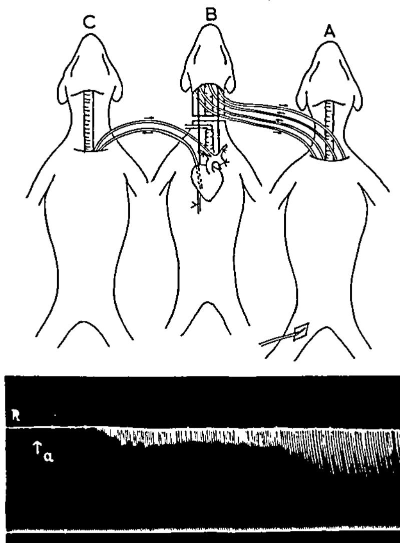


FIG 56 *Upper* The isolated head of dog B is perfused by dog A Only the vagi aortic nerves connect the head of B with its trunk Dog C is used to perfuse the cardio-aortic area of dog B The carotid artery of dog C supplies blood to the ascending aorta of dog B and the blood circulating through the coronary system of dog B is returned from the right ventricle via a cannula to the jugular vein of dog C

Lower Respiratory movements of head B a = asphyxia of dog C and heart aortic arch area of dog B —Stimulation of respiratory centre of head B —(J F and C Heymans 1927)

tied A common carotid artery of (B) was anastomosed by a Payr cannula with the cardiac end of a jugular vein of dog (C) and the cardiac end of the common carotid artery of (C) was anastomosed with an external jugular vein of (B) The heart and lungs of (B) were thus supplied with carotid blood from dog (C) Artificial ventilation of the trunk

of (B) was therefore superfluous When dog (C) was asphyxiated the cardio pulmono aortic area was supplied by blood of low pH low pO and high pCO The movements of the alae nasi of the isolated head became greater In a modification of this arrangement dog (C) was used to supply arterial blood to the lungs only by anastomosing the pulmonary artery of (B) with the carotid artery of (C) and the pulmonary vein of (B) with the external jugular vein of (C) No change in the respiratory activity of the isolated head occurred when asphyxial blood from (C) traversed the pulmonary circuit of (B) Hence the pulmonary vessels were not the site of the chemoreflexes Lastly

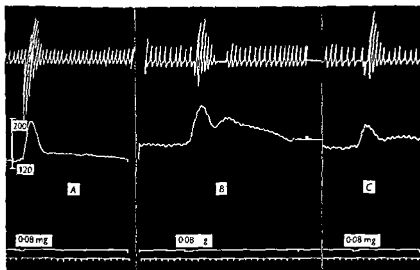


Fig 57 Cat Chloralose anæsthesia At signal 0 08 mg nicotine was injected intraventricularly A vagi and aortic nerves intact B vagi cut C left aortic nerve cut leaving right aortic nerve intact —(E Neil C R M Redwood and A Schweitzer (1949) *J Physiol* 109 392)

in a third variation of the three dog experiment the blood from dog (C) was permitted to traverse only the heart and aortic arch of dog (B) This was effected by anastomosing the carotid artery of (B) with the carotid artery of (C) and the right ventricle of (B) via a catheter with the external jugular vein of (C) Blood thus passed from the carotid artery via the aortic arch into the coronary arteries and thence to the right ventricle from which it returned to the donor dog At the moment of beginning the retrograde perfusion of the aortic arch and heart the two lung roots were ligated Asphyxia of dog (C) led to reflex changes of respiratory activity in the head of (B) which must have been due to the stimulation of chemoreceptors situated in the heart or in the aortic arch or in some tissue supplied by vessels which arose from these structures (Fig 56)

In 1939 Comroe developed the technique of retrograde catheterization of the carotid and subclavian arteries A catheter was pushed via one of these arteries into the aortic arch The tip of the catheter could if necessary be inserted through the aortic valves into the left ventricle Small doses of sodium cyanide (which stimulates the chemoreceptors) were injected via the catheter and the respiratory and blood pressure changes which

occurred were recorded The doses given were so small that chemoreflex responses only occurred if the tip of the catheter were adjacent to the origin of the arterial vessels which supplied the aortic chemoreceptors Comroe found that to activate the chemoreflex responses of hyperventilation and hypertension in the dog by the injection of sodium cyanide the tip of the catheter had to be in the ascending arch of the aorta Injections made when the catheter tip was in the transverse part of the aortic arch were ineffective Hence he concluded that the arterial supply of the aortic body arose from the first part of

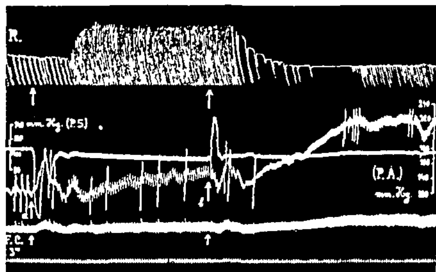


FIG 58 Perfusion of the isolated but innervated carotid sinus areas (chemoreceptors) of a dog R = respiratory movements and amplitude P S = perfusion pressure of carotid sinus areas P A = blood pressure of dog F C = heart rate of dog *a* = perfusion of carotid sinus areas with Ringer solution pH 7 3 but containing 61 64 vol per cent CO_2 instead of Ringer solution pH 7 4 containing 19 8 vol per cent CO_2—Marked reflex hyperpnea and rise of arterial pressure *b* = perfusion of carotid sinus areas with Ringer pH 7 3 containing 19 8 vol per cent CO_2—First apnea and further return to normal breathing —(C Heymans J J Bouckaert and L Dautrebande (1930) *Arch int Pharmacodyn* 39 400)

the transverse arch Gernandt (1946) repeated Comroe s experiments in the cat and found that the aortic chemoreflexes could only be excited by injecting lobeline or cyanide into the left ventricle (i e with the catheter tip within the cavity) This confirmed Comroe s findings in the cat both authors concluded that the arterial supply of the chemoreceptors arose from the coronary arteries Neil and co workers (1949*c*) confirmed these results (Fig 57) and showed that the chemoreceptor fibres passed up both left and right vagi and aortic nerves the preponderance of chemoreceptor fibres lay on the right however This was the conclusion from experiments similar to those of Comroe in which the response to intraventricular injections of lobeline was checked before and after successive section of both vagi and aortic nerves

In none of these experiments was any response obtained by injecting lobeline or cyanide in the vicinity of the right subclavian artery The right aortic glomus separately described by Muratori Nonidez & Howe has not yet been proved to be chemoreceptor in function although this is most likely due to its difficulty of access

Carotid Chemoreceptor Reflexes

At about the same time that J F & C Heymans had succeeded in demonstrating the cardio aortic reflexogenic zones de Castro had suggested that the carotid body might sample the chemical composition of the blood Unaware of this paper at the time C Heymans & J J Bouckaert began an intensive investigation of this very possibility

The carotid bifurcation was isolated and was perfused either by a donor dog or a Dale Schuster pump Perfusion of blood equilibrated with a low pCO tension caused reflex depression of breathing conversely the perfusion of blood with high pCO excited

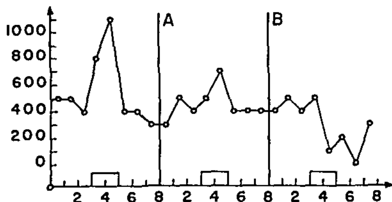


FIG 59 Cat decerebrated Abcissa = time in minutes Ordinate = respiratory volume per minute air replaced 8 / O in N_2 during test periods Left = normal respiratory responses A = respiratory responses after section of vagi aortic nerves B = respiratory response after section of vagi aortic and carotid sinus nerves —(J J Bouckaert K S Grimson C Heymans and A Samaan (1941) *Arch Intern Pharmacodyn* 65 63)

the respiration (Fig 58) Section of the corresponding sinus nerve abolished these responses Heymans & Bouckaert also found that the perfusion of anoxic blood caused reflex hyperpnœa Thus when a donor dog (which was used to supply blood for the carotid bifurcation area of a recipient) was rendered anoxic by the inhalation of nitrogen intense respiratory stimulation of the recipient (B) took place The response was abolished by sinus nerve section In further experiments Heymans *et al* (1931 1933) showed that section of the sinus and vagus nerves converted the hyperpnœa provoked by oxygen lack in the intact animal to respiratory depression (Fig 59) Oxygen lack was thus proved to excite the breathing solely by chemoreceptor stimulation This conclusion has been widely confirmed None of these experiments proved the actual site of the chemoreceptor tissue in the bifurcation region At first attention was directed towards proving that the chemoreceptors were anatomically separate from the baroreceptors Bouckaert Dautrebande & Heymans (1931) thus ligated the nerve fibres leaving the sinus region between the carotid body (lying on the base of the occipital artery) and the carotid sinus itself This abolished the responses of the carotid bifurcation to pressure changes but did not affect those to chemical stimulation Camus Benard & Merklen (1934) confirmed these findings by actually cutting the sinus nerve between the carotid body and the sinus Selective inactivation of chemoreceptor tissue by the intra carotid injection of lycopodium (which embolised the glomus capillaries) was first reported by

Heymans & Bouckaert (1933), pressoreceptor sensitivity was not affected Schmidt (1932) found that ligation of the occipital artery at its origin abolished or reduced the reflex effects evoked by altering the chemical composition of the blood in the carotid bifurcation area Gollwitzer Meier (1934) obtained similar results as did de Bettencourt & Cardoso (1937) Gollwitzer Meier showed that a ligature tied between the sinus and the origin of the occipital artery (ligature 6) abolished the response to intra-carotid injection of chemo receptor tissue stimulants but neither of these workers could decide whether the chemore ceptors were located in the carotid body or in the first part of the occipital artery Comroe & Schmidt (1938) were the first to claim that the effects of intra carotid injections of small doses of lobeline or cyanide were abolished after clamping the small artery to the carotid body and restored on opening this vessel This must have been a very fortunate prepara tion for *in our considerable experience and in that of Chungcharoen Daly & Schweitzer* (1952*a*) the carotid body is usually supplied by three or four arteries which do not necessarily originate from the occipital artery Bouckaert & Pannier (1942*a*) confirmed the localization of the chemoreceptors in the glomus and that of the baroreceptors in the sinus

Electroneurographic Evidence of Chemoreceptor Activity

Shortly after the observation of Heymans Bouckaert & Dautrebande (1930) that reflex hyperpnœa occurred when anoxic or hypercapnic blood perfused the carotid bifurcation area Bronk (1931) Bronk & Stella (1932) and Heymans & Rijlant (1933) examined the impulse activity of the sinus nerve Heymans & Rijlant described increased activity in the nerve during asphyxia of a rabbit which they were unable to attribute to any difference in the blood pressure Bronk & Stella however obtained only baro receptor fibres which were uninfluenced by the chemical environment Bronk in a per sonal communication to Stella (see Bogue & Stella 1935) noted an occasional discharge from the intact nerve of the rabbit which appeared during anoxia and which persisted after death Bogue & Stella (1935) pointed out that Bronk s findings and those of Heymans & Rijlant might be merely due to irregular discharges from the baroreceptors themselves abnormally excited by the conditions of the blood They cited the results of Matthews (1933) who reported that the muscle spindles discharged spontaneously often at high frequency as the result of occlusion of the circulation They therefore re investigated the problem The sinus nerve was cut centrally They stripped the carotid at the bi furcation and obtained preparations of the sinus nerve which contained only one or two sinus (baro) receptors On asphyxiating the animal or on producing anoxia they claimed that an increase occurred in the impulse activity of the nerve which was not referable to the baroreceptors but the records obtained are difficult to interpret They noted that the impulse activity ensuing upon complete interruption of the circulation of blood through the sinus bifurcation (which they ascribed to chemoreceptor discharge) might persist for as long as thirty minutes In a later paper Samaan & Stella (1935) found that multi fibre preparations of the sinus nerve which did not contain baroreceptor fibres showed an increased impulse activity on raising the CO_2 tension of the arterial blood from 35 mm Hg to 50 mm Hg Further rise of CO_2 tension to 72 mm Hg caused an even greater outburst of impulses Samaan & Stella concluded that at or below 32–35 mm pCO_2 the chemo-receptors were at rest discharging progressively more frequently as the CO_2 tension rose

They confirmed the finding of Bogue & Stella (1935) that arrest of the circulation caused chemoreceptor discharge and interpreted in this light Schmidt s result (1932) of reflex hyperpnœa on stopping the perfusion pump in an isolated sinus preparation

None of the records produced hitherto had been very impressive In 1935 Zotterman published greatly superior records of impulse activity in the IXth nerve which left no doubt in most people s minds as to the existence of chemoreceptors Euler Liljestrand & Zotterman (1939) considerably extended these early studies and obtained pure chemo receptor preparations in which they showed (*a*) some chemoreceptors active at CO tensions even below 30 mm Hg (*b*) some tonic discharge of chemoreceptors in cats breathing room air spontaneously (arterial oxygen saturation 89–92%) Even at 96% saturation of the arterial blood with oxygen there was some slight discharge of the chemo receptors which could not be referred to CO_2 effects because such animals were deliberately over ventilated to exclude such a cause

Schmidt & Comroe (1940) argued that there was no actual evidence in the published reports to prove that the impulse activity recorded was in fact occurring in chemoreceptor fibres In the animal used (the cat) the carotid body lies in the bifurcation of the carotid imbedded in the fibres from the carotid sinus not anatomically separated as in the dog The latter animal has been tried by several groups of workers to the personal knowledge of the reviewers and none have been able to duplicate the above observations although the anatomical situation is much more favourable for such an experiment than in the cat The possibility that electrical disturbances picked up in the sinus nerve may have originated in some part of the sympathetic nervous system appears not to have been considered though it seems only reasonable that if such studies are to be used to elucidate chemoreceptor activity it is incumbent on those who so use them to start by proving beyond reasonable doubt that the activity studied arose from the chemoreceptors and could not have originated anywhere else

In 1955 Aviado & Schmidt wrote in this animal (the cat) the carotid body is not as widely separated from the carotid sinus as it is in the dog but skilled hands apparently can completely divide the fibres from the pressoreceptors while sparing some of those from the chemoreceptors—a goal which could not be attained in the dog (Schmidt & Larrabee unpublished) although the anatomical situation is more favourable

This persistence in referring to the more favourable anatomical situation in the dog is misplaced Perhaps it is best to describe how the chemoreceptor preparation is made for electroneurographic recording—in the cat (or the dog) The preliminary exposure of the bifurcation is done with the aid of a 5 – 10 × magnification provided by a dissection microscope The venous drainage of the carotid body which is very obvious is carefully preserved The sinus nerve is identified and dissected clear of the surrounding fascia from its junction with the glossopharyngeal nerve up to the position of the carotid body Usually it lies lateral to or dorsal to one of the branches of the ascending pharyngeal artery (Fig 60) No attempt is made to interfere with the tissue between the carotid body and carotid sinus The nerve is cut as far centrally as possible and the cut end is held up carefully in delicate forceps The sheath of the nerve is now stripped backwards for 1 cm or so (towards the carotid body) with a firm movement This gives far better results than nibbling at the sheath in an attempt to do less damage

The sinus nerve contains some 700 myelinated fibres of these the great majority are less than 5μ in diameter Some of these are chemoreceptors and some baroreceptors The nerve is again held up by forceps with the one hand and twigs are peeled off backwards from the main trunk by a second pair of forceps These twigs should be preferably at least a centimetre long so as to allow a suitable length of nerve to be placed on the recording electrodes Each twig is successively tested for activity by placing on the recording electrodes The choice is of course random It is likely that each twig will contain some chemoreceptors and some baroreceptors but the question is whether the majority of the fibres are viable or not If the trauma inflicted has been too great then perhaps only a few fibres survive in a mass of dead tissue The electrical resistance of such a

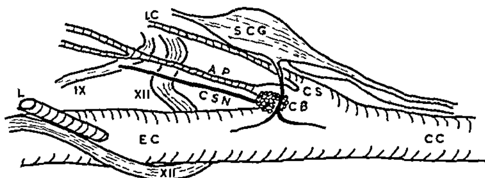


Fig 60 Right carotid sinus of cat (diagrammatic)
Key CC = common carotid artery CS = carotid sinus EC = external carotid artery L = lingual artery AP = ascending pharyngeal artery IC = internal carotid artery XII = hypoglossal nerve IX = glossopharyngeal nerve CSN = sinus nerve SCG = superior cervical ganglion

preparation is so high that the signal to noise ratio is very poor and the few action potentials from the viable fibres peep shyly above a heavy background of electrical mush Any electrophysiologist has seen this all too often If however a good preparation has been obtained then the activity is recorded photographically simultaneously with the arterial blood pressure or the e c g Baroreceptor fibres show impulse activity which occurs phasically with the pulse Temporary occlusion of the common carotid artery abolishes or reduces such discharge A rise of blood pressure caused by adrenaline injection increases the impulse activity Chemoreceptor fibres on the other hand generally show sporadic activity which bears no relation to the pulse By allowing the animal to breathe 10% O_2 in N_2 or by temporarily occluding the tracheal cannula the impulse activity increases (Fig 61) Occlusion of the common carotid artery causes an increase in the chemoreceptor discharge (Fig 21) The intracarotid injection of small doses of sodium cyanide or lobeline causes a massive discharge Having obtained a promising preparation it is most likely that the branch must be further subdivided in order to obtain as high a signal to noise ratio as possible or in order to reduce the number of active units so that their properties can be studied more discriminately The danger lies now in destroying the active units by the extra mauling inflicted It is wise to employ magnification up to 30–50× at this stage Finally a suitable preparation may be obtained There

is no disadvantage in having one or two baroreceptor units in a preparation made for the study of chemoreceptors—indeed I personally prefer to have some information from such a baroreceptor as to the heart rate or the level of the blood pressure which is thus signalled by the loud speaker

The difficulty with the sinus nerve of the dog is due to the large amount of connective tissue which binds the nerve bundles together and the numerous little blood vessels which course among the bundles This makes every stage of the preparation as described above

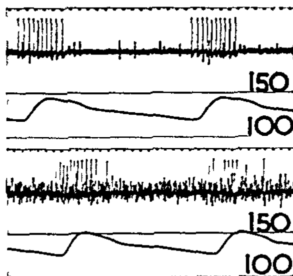


FIG 61 Cat Thiopentone anæsthesia Right sinus nerve cut centrally and a thin slip laid on saline wick electrodes Action potentials recorded on oscillograph via resistance-capacity coupled amplifier Blood pressure recorded from femoral artery by condenser manometer Records from above downwards time trace 50 c/s electroneurogram of thin slip of sinus nerve blood pressure Calibration lines for pressures of 150 and 100 mm Hg are shown A = Cat breathing air spontaneously B = Cat breathing 10 per cent O in N spontaneously Note increase in chemoreceptor activity during anoxia —(Neil)

much more troublesome The increased damage inflicted causes a large proportion of fibre preparations to show a low signal to noise ratio It is for this very good reason that the cat or the rabbit is used in the great majority of studies on chemoreceptor activity Euler & Zotterman (1942) and McCubbin Salmoiraghi Green & Page (1956) have however published perfectly satisfactory records of chemoreceptor impulse discharges in dogs The anatomical advantage of the separation between carotid body and sinus in the dog is irrelevant Schmidt & Larrabee presumably recorded from the whole carotid sinus nerve having cut such of the baroreceptor fibres as they could find running between the carotid body and the bifurcation The result is a preparation which already contains many dead fibres which are scattered through the trunk The signal to noise ratio is therefore low To achieve a reasonable preparation for the study of chemoreceptors the same procedure as detailed above must be carried out so no advantage is gained

It is very easy to show in the cat that the carotid body is the sole site of these chemoreceptor impulses It can be removed by dissection under magnification, both Landgren (1952*a*) and Neil (1952) have often done this deliberately in order to exclude chemoreceptor activity from fibre preparations As a corollary it is fatally easy to obtain a preparation which is irresponsive to chemoreceptor stimulants by damaging the venous drainage of the carotid body during dissection steady chemoreceptor discharge ensues which is unaffected by varying the chemical composition of the blood in the bifurcation area This discharge is due to stagnant anoxia

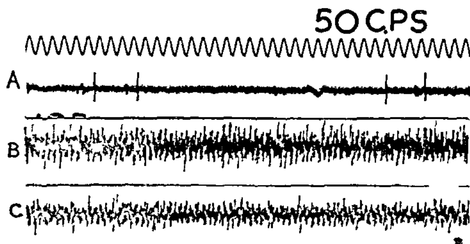


FIG 62 Cat 3·0 Kg artificial ventilation with room air Left sinus nerve cut centrally and a twig containing chemoreceptor fibres and only one baroreceptor fibre laid on electrodes.
A Control B P 105 mm Hg. baroreceptor impulses shown in each of two cardiac cycles Chemoreceptor impulses absent Time 50 C P S
B After hæmorrhage (50 ml) B P 55 mm.Hg Heavy chemoreceptor impulse traffic
C Immediately after cutting the left sympathetic trunk B P 55 mm Hg Note reduction in chemoreceptor impulses —(W F Floyd and E Neil (1952) *Arch int Pharmacodyn* 91 230)

The carotid bifurcation is supplied by a large branch of the superior cervical ganglion of which some fibres pass to the carotid body itself or to the vessels which supply it (Fig 60) The chemoreceptor discharge from the carotid body in resting conditions is almost unaffected by removal of the superior cervical ganglion and its post ganglionic branches This disposes of Schmidt & Comroe s criticism In any case as Bernthal pointed out (1944) the impulse frequency recorded by Euler Liljestrand & Zotterman (1939) far exceeded that ever seen in sympathetic fibres (see Bronk *et al* 1936 1940 Pitts *et al* 1941 Folkow 1952 Celander 1954)

Gernandt (1946) recorded action potentials in the aortic nerve which increased in number during anoxia or asphyxia or which alternatively were produced by the intra ventricular injection of lobeline or piperidine He reasonably assumed these to be chemo receptor impulses Diamond & Howe (1956) proved beyond doubt that some chemoreceptor fibres coursed in the left aortic nerve of the cat

Landgren & Neil (1951) identified the chemoreceptor discharge following severe hæmorrhage as being due to the reduction in blood flow through the carotid body The

activity of the chemoreceptors becomes enormous when the mean blood pressure falls from normal levels to about 50 mm Hg (Fig 62) They attributed this activity to stimulation of the chemoreceptors by stagnant anoxia Floyd & Neil (1952) showed that the chemoreceptor discharge following severe hæmorrhage was not greatly affected by section

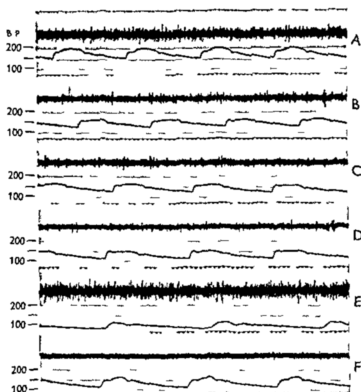


FIG 63 Cat 3 8 kg chloralose urethane anæsthesia Spontaneous respiration Left carotid sinus nerve cut centrally all baroreceptor fibres removed by dissection Right carotid artery cannulated for recording blood pressure Records on each strip from above downwards time (50 c/s) electroneurogram and arterial blood pressure Blood pressure calibrations (mm.Hg) are shown on left of each film strip A = breathing 5 per cent O_2 in N_2 B = breathing 100 per cent O_2 (note reduction of chemoreceptor activity) C = after 5 minutes breathing 1 per cent CO in O_2 (CO saturation = 25 per cent) D = after 30 minutes breathing 1 per cent CO in O_2 (CO saturation = 70 per cent) After 31 minutes inhalation of 1 per cent CO in O_2 5 per cent O_2 in N_2 was substituted as the inspired gas E = after 5 minutes breathing 5 per cent O_2 in N_2 (CO saturation = 76 per cent) F = after 2 minutes breathing 100 per cent O_2 Note the very slight chemoreceptor activity in D compared with the intense discharge in E —(H N Duke J H Green and E Neil (1952) *J Physiol* **118** 520)

of the local sympathetic nerve supply to the glomus (Fig 62) The reduction in blood flow through the carotid body was therefore considered to be largely passive due to the fall in systemic pressure Duke Green & Neil (1953) supported the earlier experimental results of Comroe & Schmidt (1938) in direct recordings of chemoreceptor impulse activity during the development of carboxyhæmoglobinæmia The reduction in oxygen content of the blood caused by the increasing concentration of carboxyhæmoglobin caused no excitation

of the chemoreceptors as long as the tension of oxygen in the blood did not fall (*Fig* 63) Comroe & Schmidt (1938) had proved earlier that reflex excitation of the breathing could not be produced from the carotid body by perfusing carboxylated blood unless the oxygen tension of that blood was low Grebenkina (1953) however disagrees with this

Paintal (1953) alone has measured the conduction velocity of chemoreceptor fibres In the aortic nerve such fibres conduct impulses at about 10 m /sec (range 7–12)

Cross & Malcolm (1952) have demonstrated that the chemoreceptors are *sensitive* to anoxia in the sheep fœtus by recording action potentials from the sinus nerve The *two* fœtal lambs were operated on under chloralose anæsthesia given to the mother and remained attached via the umbilical cord Oxygen mixtures were given to the mother when the lambs were about a week short of full term Kittens *in the first few days of* post natal life and a piglet born the same day showed active chemoreceptor *responses to* anoxia Baroreceptor activity was found in the fœtal lambs and in *the other animals* Clark (1934) showed that the fœtus possessed no baroreceptor reflexes until *shortly after* birth Cross & Malcolm (1952) considered that their results were in *keeping with the* demonstration by Cross & Oppe (1952*b*) that premature infants possessed an active chemoreceptor reflex The premature baby however does not maintain anoxic *hyperpnœa* for more than two minutes on 15% oxygen as central depression occurs

CHAPTER 16

THE CHEMICAL CONTROL OF RESPIRATION

The Development of the Concept of "Centrogenic" and "Reflexogenic" Mechanisms

FOLLOWING the discovery by Legallois (1812) of the medullary respiratory centre and its confirmation by Flourens (1824) interest developed as to the mode of excitation of this centre in the intact animal It was found that the rebreathing of small volumes of air caused great hyperpnœa followed by cessation of breathing Similar results were obtained by Kussmaul & Tenner (1857) on shutting off the cerebral blood supply They observed that the blood remaining in the cerebral vessels became venous in appearance Rosenthal (1862) noted that excessive artificial respiration of an animal was followed by a temporary respiratory arrest which he designated as apnœa He later concluded (1882) that the chemical control of the respiratory centre was exercised by the oxygen content of the blood If this was low hyperpnœa resulted and conversely if the oxygen content was raised by over breathing respiratory activity ceased As Haldane (1922) has said the weak point in his argument lay in the fact that there is no apnœa on breathing oxygen even though the oxygen content of the blood is thereby raised considerably above that seen normally Traube (1862) showed that apnœa could be produced even by breathing nitrogen and could not therefore be due to over arterialization of the arterial blood Pfluger (1868) showed that both an excess of CO and a lack of O could excite the medullary centre but considered that oxygen deficiency was the more important Paul Bert (1878) investigated the effects of low barometric pressure on the respiration and proved that the respiratory effects produced by CO and O_2 were due to the pressure of these gases in the air breathed Walter (1877) was the first to note the hyperpnœa caused by acidæmia induced by the administration of hydrochloric acid intravenously or into the stomach Miescher Rusch (1885) directed attention to the great sensitivity of the respiratory centre to a slight increase in the CO percentage in the inspired air On the other hand he showed that a corresponding diminution in the oxygen content of the air had no effect on the breathing He concluded that the CO_2% in the air in the lungs was the ordinary determinant of the state of respiratory activity Geppert & Zuntz (1888) however showed that the tetanization of hind limb muscles by faradic stimulation caused hyperpnœa in animals in which the spinal cord was transected They found that the CO_2 content of the arterial blood was lower and the O content was higher than normal They concluded that some product of metabolism of the active muscles gained access to the blood stream and on being carried to the respiratory centre excited it They referred to the results of Walter and suggested that the metabolite formed in the active muscle was an acid

Haldane & Lorrain Smith (1893) found that the hyperpnœa caused by rebreathing air in a closed circuit was due to the rise in the partial pressure of CO Thus when the proportion of CO_2 in the air rose to about 3% and the oxygen fell to about 17% the

breathing showed a noticeable increase and when the CO_2 level rose to 6% (O =13%) the panting became exhaustingly severe When the experiment was repeated with the difference that the CO_2 was absorbed by soda lime the breathing showed no increase until the oxygen level reached 14% Lastly when rebreathing of pure oxygen or high oxygen mixtures was carried out and the CO was again allowed to accumulate the hyperpnœa became intolerable when the CO_2 level reached 8 9% despite the fact that the oxygen level was abnormally high These results therefore supported the views of Miescher Rusch Leon Fredericq (1901) then showed in his famous crossed circulation experiment that the composition of the arterial blood directly affected the respiratory centre He cross-connected both the carotid arteries and the jugular veins of two dogs so that the head and therefore the brain of each dog received the greater part of its blood supply from the other dog If one dog was asphyxiated the other dog showed hyperpnœa Conversely hyperventilation of one dog induced apnœa in the other

It was not however until Haldane & Priestley (1905) introduced their method for the direct determination of alveolar gas tensions in man that the delicacy of control exercised over the breathing by the alveolar tension of carbon dioxide was appreciated Using this method they showed that under ordinary physiological circumstances the alveolar CO tension was kept almost constant at about 40 mm Hg Moreover this constancy was observed even between barometric pressures of 4,640 and 300 mm Hg provided that oxygen lack was avoided at the lower pressures by enriching the inspired gas with oxygen (Hill & Greenwood 1906 Boycott & Haldane 1908) A maintained increase of about 1½ mm Hg in the alveolar pCO doubled the respiration and conversely apnœa resulted when the alveolar pCO fell by the same amount Oxygen lack proved to be a much less effective stimulus—it was not until the alveolar pO fell to about 55-60 mm Hg (%O =8 9) that the breathing was noticeably stimulated This alveolar percentage corresponds roughly to an inspired oxygen percentage of 14% ($pO_2 \approx 100$) Hyperpnœa induced by anoxia was shown to cause lowering of the alveolar pCO Meanwhile Araki (1894) had found considerable amounts of lactic acid in the urine of animals subjected to anoxæmia by the inhalation of carbon monoxide Galeotti (1904) had shown that the titration alkalinity of the blood was markedly decreased at high altitudes These two results were taken to mean that anoxæmia caused lactacidosis Boycott & Haldane (1908) therefore advanced the theory that the hyperpnœa of anoxia was due to lactacidosis lactic acid being supposed to act in the same way as did carbon dioxide The action on the respiratory centre of the circulating blood is due to what may be called its total acidity including of course that due to free CO_2 If more lactic or other acid or less alkali is present in the blood than usual, then less free CO_2 will be required to excite the respiratory centre and vice versa

Winterstein (1911) advanced his first reaction theory in which he claimed that the arterial cH was the common stimulus of respiratory activity At the time no reliable measurements of cH had been made but Hasselbalch (1912) promptly introduced the hydrogen electrode method and used it to show that by varying the diet he could induce considerable changes in the alveolar pCO_2 whereas the arterial cH remained virtually unchanged The blood reaction theory thereby gained widespread acceptance Hasselbalch also made important contributions to the application of the Arrhenius dissociation theory to the problems of acid base equilibrium of the blood (which had been begun by

L J Henderson (1909)) The Henderson Hasselbalch equation —

$$pH = pK_1 + \log \frac{(NaHCO_3)}{(H_2CO_3)}$$

was an important milestone Acidosis could thus be due to a high pCO (H_2CO_3) or a low ($NaHCO_3$) Alkalosis on the other hand could be primarily non gaseous (raised $NaHCO_3$) or primarily gaseous (low H CO_3 or pCO)

Zuntz Loewy Muller & Caspari (1906) Durig Kolmer Rainer Reichel & Caspari (1909) had found that the resting alveolar pCO_2 at an altitude of about 15 000 ft (Monte Rosa) was below normal and Douglas Haldane Henderson & Schneider (1913) confirmed this with their results obtained on Pike s Peak (14 109 ft) Barcroft Camis Mathison Roberts & Ryffel (1914) and Douglas *et al* (1913) however did not find sufficient lactacidæmia at 14–15 000 ft to explain the hyperpnœa and suggested that anoxia caused excretion of base by the kidney which thereby induced acidosis

Hasselbalch & Lindhard (1915) were the first to show electrometrically that after prolonged exposure to anoxia there was no significant change in the blood pH Winterstein himself (1915) was the earliest to report that acute anoxia on the other hand caused alkalosis this finding of course necessitated revision of his first reaction theory Before he issued his second formulation in 1921 the true solution of the problem of anoxic hyperpnœa was independently given by Haldane Kellas & Kennaway (1919) and by Henderson (1919) and Haggard & Henderson (1920) Haldane *et al* & Henderson showed that the decrease in bicarbonate concentration in the blood in anoxia was not due to acidosis at all but was secondary to the effects of hyperventilation which in turn was due to stimulation of the respiratory mechanism by the oxygen lack itself Henderson & Haggard (1918) had shown in animal experiments that by merely varying the ventilation of the lungs and thereby adjusting the pCO_2 of the arterial blood they could reduce the bicarbonate content of the blood Haldane *et al* (1919) showed that hypoxic hyper ventilation was followed by a reduction in the renal excretion of acid and ammonia The renal response was secondary to the gaseous alkalæmia and served to restore the blood plasma pH It was now appreciated that the gaseous alkalæmia induced by anoxic stimulation of the respiratory mechanism would tend to check the hyperpnœic response to the oxygen lack The increased excretion of alkali and diminished formation of ammonia (by the kidney) lead gradually towards a compensation of the alkalosis and simultaneous relief of the anoxæmia this relief being due to the increased oxygen supply to the lung alveoli But the final result is a compromise A certain small degree of anoxæmia and consequent alkalosis still remains as evidence by the fact that on removal of the anoxæmia there is quite an appreciable immediate rise in the alveolar CO pressure as was shown for instance when we breathed air enriched with oxygen after we had become acclimatized on Pike s Peak The supposed acidosis is thus not an acidosis at all but the inadequate compensation of an alkalosis (Haldane 1922)

Very careful observations were made by Miss Fitzgerald (1914) of the alveolar pCO_2 values of acclimatized inhabitants of many altitudes up to 11 000 ft She found a linear relationship between the alveolar pCO_2 and the barometric pressure with a decrease of 4 2 mm Hg of pCO per 100 mm Hg decrease in barometric pressure As the basal metabolic rate is not affected by altitude this implies that the pulmonary

ventilation of the acclimatized dwellers increases steadily *proportionally to the degree of* oxygen want At 14 000 ft however the barometric pressure is 450 mm and the inspired pO_2 is therefore about 90 mm As Boycott & Haldane (1908) showed this degree of anoxia has no effect on the breathing of a subject acutely exposed to it The development of hyperpnœa in mild anoxia therefore requires time

Winterstein (1921) introduced his second reaction theory which *stated that the* respiratory activity was controlled by the cH within the respiratory centre neurones themselves In oxygen deficiency *he suggested that there was a local acidosis in the respiratory centre*, induced by the intracellular formation of lactic acid This suggestion was supported by Gesell and his school and Gesell (1923) stated that the activity of the respiratory centre was fundamentally a function of its own intracellular acidity as opposed to the reaction of the arterial blood the specificity of CO and the direct stimulating action of lack of oxygen (See also Gesell, 1925 1929 and Haldane 1927)

At this time a controversy raged as to whether CO exerted a specific action on *the respiratory centre* or whether it merely stimulated the centre by acting as an acid Jacobs (1920) provided a valuable clue as to the action of CO on the interior of plant and animal cells He observed that saturated solutions of carbon dioxide were much *more poisonous for protozoa* or tadpoles than were other solutions of acids of the same pH Even when a saturated solution of CO_2 was brought to neutrality by the addition of sodium bicarbonate the same poisonous action was noted He attributed this to the great diffusibility of CO He pointed out that CO_2 penetrated the cell membrane much *more rapidly* than the hydrogen ion The flower *symphytum peregrinum* possesses petals which are pink in acid solution and blue in alkaline solution when placed in a solution of CO in 0 5M $NaHCO_3$ (pH 7 4) the flower became pink Placed in distilled water of pH 5 the flower remained blue Similar experimental results were obtained using sea urchin eggs coloured pink with neutral red These were placed in three solutions 0 5M NaCl with a trace of sodium bicarbonate 0 5M $NaHCO_3$ saturated with CO and 0 5M NH_4Cl with a little ammonium hydroxide In the first solution the colour of the eggs remained unchanged in the second they showed an acid reaction and in the third an alkaline reaction

Collip (1920) noted that the injection of bicarbonate into the blood stream caused a biphasic respiratory response i e initial hyperpnœa followed by depression of the *respiration* The pH of the plasma was shifted to the alkaline side Gesell & Hertzmann (1926) showed that the intravenous injection of bicarbonate caused both a shift of the plasma pH to the alkaline side and at the same time a change of pH of the *c s f* to the acid side Winterstein (1956) has since referred to this as an excellent repetition of Jacobs s experiments applied to mammals The membrane of the sea urchin egg is replaced by the so-called barrier between the blood and cerebrospinal fluid Evidently the effect on the respiratory centre depends on the pH of the c s f as well as on the pH of the blood *In* Gesell s experiment the undissociated carbon dioxide produced by the dissociation of the bicarbonate ion diffuses through the barrier and causes acidity on the other side (Winterstein 1956)

The discovery of the chemoreceptor respiratory reflexes by Heymans and his colleagues (1926–1931) necessitated some revision in the hypotheses advanced to explain the chemical control of respiration The effect of anoxia in causing stimulation of the

breathing was shown to be entirely dependent on chemoreflex stimulation of the medullary neurones Haldane was curiously slow in accepting this fact and even as late as 1935 Haldane and Priestley stated that the carotid body had not been proved to stimulate the respiratory mechanism in anoxia except by causing changes in the circulation

Heymans strongly supported the view that the chemoreceptors were more sensitive to carbon dioxide than was the centre Many have since challenged this opinion notably Schmidt (1941) and Comroe & Schmidt (1940 1941) and there are few nowadays who hold that this viewpoint is correct Winterstein in a further attempt to group the chemical factors which stimulated respiration as producing the single common change of intra cellular acidity now included the carotid and aortic bodies in his scheme by stating that

Table II

Dog	Condition	Blood pH	C S F pH
1	normal	7 47	7 18
	15 min after NH_4Cl	7 47	7 28
2	normal	7 58	7 37
	15 min after NH_4Cl	7 39	7 38
	4 hours later	7 53	7 21
3	normal	7 51	7 38
	30 min after NH_4Cl	7 48	7 44
4	normal	7 53	7 36
	15 min after NH_4Cl	7 46	7 36
10	normal	7 44	7 22
	90 min after NH_4Cl	7 36	7 29

they too were stimulated in this manner There is no doubt that they are stimulated by *acidæmia but there is little evidence that the various chemical changes which affect them* act thus

The strongest supporter of the belief that CO exerts a specific action on the breathing has been Nielsen Nielsen (1936) showed that the inhalation of CO mixtures caused intense hyperpnœa but little change in arterial pH metabolic acidosis on the other hand caused marked changes in arterial pH but little change in the breathing In one of his subjects the inhalation of CO caused an increase of 10 litres per minute in the resting pulmonary ventilation with a lowering of the arterial pH of 0 04 whilst during ammonium chloride ingestion the arterial pH decreased by as much as 0 08 but the breathing increased by only 0 3 litres per minute Nielsen made his observations on states of acidosis which *lasted as long as ten days in some cases—they were therefore steady states and as* Schmidt (1941) has said it is inconceivable that there could have been failure of the cells of the respiratory centre to come into equilibrium with the arterial blood with respect to hydrogen ions Unfortunately for the conclusions based by Nielsen on these experiments the drug ammonium chloride exerts its effects on the respiratory mechanism in a manner more complicated than he believed J B S Haldane (1921) claimed that the metabolic acidosis caused by ammonium chloride was due to the metabolic dissimilation of the ammonium adicle by the liver which converted it to urea Winterstein & Gokhan (1953) have lately denied that this is the mechanism responsible Ammonium chloride injected intravenously into hepatectomized dogs still caused acidosis Presumably Winterstein & Gokhan do not imply that the mechanism suggested by Haldane is of *no importance*

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but rather that its contribution is a secondary one In further experiments these workers gave ammonium chloride by mouth (330–500 g /Kg/body weight/day) or by intravenous injection (50–300 mg /Kg/ in 1% solution) to normal dogs They measured the changes in pH of the blood and the cerebrospinal fluid Table II shows some of their results in dogs given intravenous ammonium chloride It can be seen that the *plasma pH fell* whereas the c s f pH rose One might comment incidentally, on the obvious disparity between the normal pH values of blood and c s f in these dogs This is contrary to the findings of Parsons & Shearer (1922) and McQuarry & Shohl (1925) in man (See also Beck & Lauber 1929 Leusen 1954)

Pulmonary ventilation was measured in these dogs and in general it was found that the increase in breathing was relatively small compared with the marked change in plasma pH The most striking finding occurred when they examined the respiratory response to ammonium chloride after denervation of the carotid bodies Instead of hyperpnœa the drug caused a depression of the breathing Table III

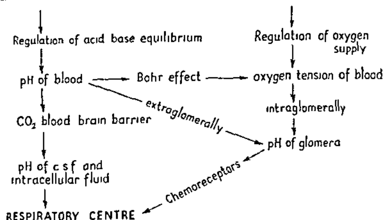
Table III

Condition	Blood pH	c s f pH	Respiratory volume
normal	7 36	7 28	5 750
After 5 days NH_4Cl	7 28	7 34	6 000
normal	7 42	7 34	6 000
After 6 days NH_4Cl	7 24	7 37	6,250
Left carotid chemoreceptors removed and right glomus denervated nine days later			
normal	7 32	7 12	4 500
After 5 days NH_4Cl	7 22	7 24	3 650
normal	7 31	7 14	4 500

The authors argue from these results that the *hyperpnœic response to* NH_4Cl is excited reflexly by chemoreceptor stimulation The hypopnœa which ensues upon ammonium chloride administration in the chemoreceptor denervated dogs they attribute to the alkalinity of the cerebrospinal fluid This rise of pH in the c s f is due to the following changes —In the blood ammonium chloride ionizes into NH_4^+ and Cl^- The ammonium ion is unstable at the blood pH and dissociates to give electroneutral ammonia (NH_3) and hydrogen ion (H^+) The electroneutral ammonia diffuses quickly into the c s f but the hydrogen ion cannot readily penetrate the barrier between the blood and the cerebrospinal fluid Once in the c s f the ammonia combines with water to form ammonium hydroxide which ionizes to give ammonium and hydroxyl ions and the reaction of the fluid becomes alkaline

Winterstein & Gokhan state The fact that in ammonium chloride acidosis after chemoreceptor denervation the respiratory centre is no longer affected by the acidity of the blood seems to prove that the barrier between the blood and the brain is identical with that between the blood and the c s f at least as far as the permeability of the hydrogen ion is concerned The fact that a barrier exists against respiratory effects is a new proof for the absence of any exciting effect of carbon dioxide itself as no such barrier exists against carbon dioxide

From these results Winterstein (1953 1956) presents his latest Reaction theory in schematic form —



Before we can attempt to evaluate the role of the chemoreceptors in breathing it is perhaps wise to consider some results of Marshall & Rosenfeld (1936) and others which suggest that anæsthetics themselves may influence the balance between centrogenic and reflexogenic respiratory activity

Marshall & Rosenfeld noted that animals deeply anæsthetized often stopped breathing when oxygen was substituted for room air as the inhalant They suggested that the chemoreceptors were driving the breathing on air owing to depression of the respiratory centre by the anæsthetic They concluded that in deep anæsthesia the respiratory control reverted to a more primitive reflex mechanism which was itself probably more fundamental in remote ancestral forms They quoted Babak (1909) who observed that the respiratory mechanism of the tadpole was extremely sensitive to changes of oxygen tension in the water but little affected by alterations of the carbon dioxide pressure Schmidt & Comroe (1940) and Schmidt (1940 1941 1945) have repeatedly drawn attention to these results They stress that anæsthetization itself alters the balance between the centrogenic and reflexogenic control of the breathing in favour of the latter It is only fair to point out however that the anæsthetic dosage used by Marshall & Rosenfeld was unduly generous They found that the inhalation of oxygen caused a marked depression of breathing or even apnœa in thirty out of thirty one cats These cats were given 150–210 mg /Kg/ body weight of phenobarbitone sodium plus 1–5 mg /Kg morphine—a dosage which is excessive Two cats which showed oxygen apnœa were anæsthetized by the injection of 200–280 mg /Kg of chloralose which is a colossal dose In our experience with ordinary anæsthetic dosage of chloralose (80–100 mg /Kg) it is very rare indeed to see respiratory arrest when oxygen is administered as an inhalant Indeed it is sometimes difficult to persuade a student class that some diminution of the breathing has occurred as a result of giving oxygen to the animal The main point which seems to arise from Marshall & Rosenfeld s results is the practical one that the chemoreceptors are of vital importance in maintaining the breathing in excessively anæsthetized patients

Dripps and Dumke (1943) administered a carbon dioxide mixture to dogs to test the respiratory centre response before and after anæsthesia and injected sodium cyanide

to assess the chemoreflex' effect on the breathing in these two circumstances A variety of anæsthetics were given in more ordinary anæsthetic dosage Thiopentone barbitone ether pentobarbitone chloralose cyclopropane and morphine all depressed the respiratory response to carbon dioxide Only ether and cyclopropane depressed the respiratory response to sodium cyanide Chloralose increased the respiratory response to cyanide whereas the other anæsthetic agents did not affect it They concluded that the use of any of the above anæsthetics other than ether or cyclopropane was likely to exaggerate the apparent importance of the chemoreceptors in the control of respiration Chloralose was cited as the most likely anæsthetic to cause an imbalance between the centrogenic and reflexogenic control as it exaggerated the chemoreflex effect and diminished the central response to carbon dioxide

At this time there was no information as to whether the respiratory neurones which responded to carbon dioxide were identical with those which were in synaptic relationship with the afferent fibres from the chemoreceptors Banus Corman Perlo & Popkin (1944) discussed this in drawing attention to the results of Comroe (1943) who had studied the respiratory effects of both electrical stimulation and local chemical excitation (by the microinjection of buffer solutions) of the floor of the IVth ventricle in the region of the respiratory centre Comroe found that certain regions when excited chemically caused respiratory responses but not when stimulated electrically and *vice versa* Banus and co workers suggested that there might be two systems in the respiratory centre ' one that originates impulses when the hydrogen ion concentration increases within the cell and one that responds to impulses coming to it in an afferent reflex way They did not assume that the two systems in the respiratory centre were necessarily to be found in separate groups of cells but postulated that they might be found in the same cell

Curt von Euler & Soderberg (1952) investigated the effect of chloralose on the response of the respiratory neurones to carbon dioxide and to chemoreceptor stimulation by lobeline Decerebrate cats were curarized vagotomized and artificially ventilated The phrenic electroneurogram was recorded and revealed the response of the respiratory neurones The response to ventilation with CO was assumed to be centrogenic that to the intravenous injection of lobeline was taken to be reflexogenic Figure 64 shows some of their results Before chloralose was given the respiratory neurones responded briskly to carbon dioxide and to lobeline After chloralose the response to carbon dioxide was greatly reduced but that to lobeline was unaltered Incidentally it was certainly not exaggerated which is in disagreement with the claims of Dumke & Dripps and the contentions of Schmidt The loss of central sensitivity to carbon dioxide despite the maintenance of the respiratory reflexes led Euler & Soderberg to conclude that the chemosensitive structures in the medulla which respond to CO could not be links in the pathways of the respiratory reflexes In further experiments they demonstrated that slow potential changes could be recorded in the medulla in the region of the respiratory centre (1952*b*) These potentials were evoked by an increase in the pCO of the blood but could not be aroused by anoxia They were independent of the state of activity of the chemoreceptor afferents but were selectively depressed by chloralose

Hoff & Breckenridge (1955) claim that it is not necessary to assume two separate groups of neurones which influence the final common neurones leading to the motor cells in the cervical and thoracic segments of the cord While Euler & Soderberg have concluded

that the medullary cells sensitive to carbon dioxide are separate from those which synapse with the chemoreceptor afferents Hoff & Breckenridge claim that a neurone may lose its spontaneous rhythmicity without altering its resting excitability to afferent stimulation and cite the results of Lorente de No (1947) on peripheral nerve to defend their argument They also refer to the recent results of Chatfield & Purpura (1953) Chatfield & Purpura exposed the floor of the IVth ventricle and stimulated the site of the inspiratory centre

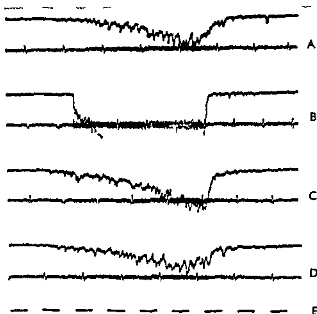


FIG 64 Phrenic efferent neurogram of decerebrate cat Both vagal nerves cut Tubocurarine Artificial respiration The upper curves the same as the lower curves after rectification and integration The lower curves disturbed by e c g Records A and B before C and D after intravenous injection of 0 05 g Chloralose/kg body weight Records A and D show the effect of 1 mg lobeline intravenously during ventilation with pure oxygen B and C show the effect of ventilation with 6 5 per cent CO_2 in O_2 Record E gives the time in 0 25 second —(C von Euler and U Söderberg (1952a) *J Physiol* 118 545)

tetanically The degree of the apneustic response was taken to indicate the resting excitability of the centre After vagotomy the apneustic response was much greater and conversely stimulation of the central end of the vagus reduced the response In the vagotomized cat carbon dioxide inhalation had no effect on the depth of the apneustic response to tetanic stimulation of the centre but increased the rhythmic mechanism so that a break through from apneusis to the normal rhythm of respiration occurred earlier in the period of electrical stimulation Thus though carbon dioxide is commonly regarded as a respiratory stimulant its stimulating action cannot be due solely to its effect on the excitability of the centre such as is conspicuously produced by vagotomy The term excitability here however refers only to the excitability of the cells to electrical stimulation it would seem rash to generalize about the effects of vagotomy in increasing the excitability of the respiratory neurones to afferent stimuli for there is no evidence that it does

Schmidt (1944) favours the view that the respiratory neurones which respond to CO are identical with those which synapse with the chemoreceptors judging by his reference to the loss of sensitivity of the respiratory centre to carbon dioxide in morphine and barbiturate poisoning as apparently due to interference by the narcotic with the most highly developed and therefore most vulnerable property of the cells of the centre leaving them still capable of being aroused by nerve impulses from the periphery provided that these are of sufficient strength This is a repetition of the theme which he developed in his thought provoking chapter in the ninth edition of McLeod s physiology text book There is however no evidence that this point of view is correct but the reader must bear in mind that two schools of thought exist—that of Schmidt Hoff & Breckenridge and others and that of the Swedish authors Euler & Soderberg (1952) and Åstrom (1952)

CHAPTER 17

THE RÔLE OF THE CHEMORECEPTORS IN EUPNŒA AND IN THE RESPIRATORY RESPONSES TO HYPERCAPNIA AND ACUTE ANOXIA

WITH the discovery of the chemoreflex effects on respiration an intensive study was made to evaluate their contribution to the control of breathing Before considering the experimental results we may pause to reflect that many facts about the chemical control of respiration were already appreciated *Among these were —*

1 The great sensitivity of the pulmonary ventilation to changes of arterial pCO
2 The low sensitivity of the respiratory mechanism to acute oxygen lack no demon strable hyperpnœa occurs until the inspired pO falls below 100 mm Hg
3 The linear relationship between alveolar pCO_2 and barometric pressure (down to 450 mm Hg) in acclimatized anoxia In chronic anoxia the breathing increases *causing a fall of alveolar pCO Renal excretion of base allows compensation for* respiratory alkalosis
4 That man acclimatized to chronic anoxia on returning to sea level does not immediately show a reduction of pulmonary ventilation despite the removal of the anoxic stimulus

As we have seen the stimulation of the respiratory mechanism by anoxia is due to the chemoreflexes As the respiratory response to anoxia is by no means a sensitive one it would seem that if the chemoreceptors contribute to the control of eupnœic breathing they are unlikely to do it by their response to anoxia From a practical point of view at least their importance lies rather in their response to moderately severe anoxia which thus reflexly induces hyperpnœa There remains the question of whether the chemoreceptors contribute to the control of eupnœic breathing by virtue of their sensitivity to the pCO or $[H^+]$ of the arterial blood Here much argument has raged Whatever may be the final answer it is true that the response of the respiratory mechanism to CO following denervation of the chemoreceptor zones (and a lot of other reflexogenic zones besides) by sino aortic nerve sections is very similar to that of an intact animal One can say that the chemoreceptors are not essential to the response of the breathing to CO this does not mean that they do not normally participate in it These two sets of results would seem at first sight to exclude the possibility that the chemoreceptors play any role at all in eupnœa Schmidt (1941 1956) has been the strongest supporter of the theory of an emergency role of the chemoreceptors However others including Heymans Stella Euler & Liljestrand Gesell Bernthal & Winterstein have expressed the opinion that the chemo receptors exert a tonic effect on respiration in eupnœic conditions Before examining the evidence for both views we may briefly note once more the complicating factor of anæsthesia It has been suggested that this tends to exaggerate the role of the chemo *reflexes We are left with a choice between the intact unanæsthetized animal in which the*

respiratory responses to changes of chemical composition of the blood can be accurately measured but which cannot themselves be rigorously studied and the anæsthetized animal in which we can rigorously study phenomena which differ from those evocable in the intact beast

Hypercapnia

Heymans Bouckaert & Dautrebande (1930) and Heymans & Bouckaert (1939) claimed originally that the chemoreceptors were more sensitive to blood with a raised pCO than was the respiratory centre itself Thus CO rich Ringer solution caused hyperpnœa when injected into the common carotid artery if the corresponding sinus nerve were intact and all efferent branches of the bifurcation were cut save those supplying the carotid body (Fig 65) Injection of the same or greater amounts of CO rich Ringer solution into the opposite common carotid artery caused no hyperpnœa if the sinus nerve were cut even though all efferent branches of the bifurcation were tied except those supplying the medullary respiratory centre (internal carotid and occipital arteries) (Fig 65) From these experimental results they concluded that the chemoreceptors possessed a lower threshold than the centre and that they were therefore responsible for the fine regulation of breathing by CO Similar results were obtained when a 2% solution of bicarbonate buffered to pH 7 30 with CO was injected into the vertebral artery and into the common carotid supplying the innervated carotid body The vertebral injection which must have reached the medullary centre was ineffective whereas the carotid injection gave a powerful response

Schmidt & Comroe (1940) objected to these interpretations First they pointed out that everything in the arrangement of the experiment favoured the carotid body receiving a high concentration of bicarbonate buffered at a (calculated) CO tension of 480 mm compared with the respiratory centre which received a more dilute solution at a lower pCO This objection is valid Secondly they drew attention to the many experimental results published during the 1930 s of comparing the pulmonary ventilation response to CO before and after cutting the sinus nerves and vagi Heymans Bouckaert & Dautrebande (1930) themselves were the first to show that the pulmonary ventilatory response to 3% CO was not much affected by section of the vagi and aortic nerves Selladurai & Wright (1932) Schmidt (1932) Euler & Liljestrand (1936) Wright (1934 1937) Stella (1935) Gemmill & Reeves (1933) Gesell & Moyer (1937) and Smyth (1937) obtained fairly similar results In a long discussion Schmidt & Comroe (1940) pointed out that only the perfusion experiments and those which required extensive preparation of the bifurcation area gave results which suggested that the peripheral chemoreceptor mechanism was more sensitive to CO_2 than was the respiratory centre It appears to the reviewers that when the results of technically sound simple experiments conflict with those of comparably sound complicated ones the burden of proof should be on the latter their simple denervation experiment gave little justification for the belief that chemo receptor reflexes play a prominent part in the organism s response to CO yet Heymans Bouckaert & Dautrebande concluded La sensibilite reflexogene respiratoire des sinus carotidiens domine la sensibilite directe du centre respiratoire aux differents excitants pression arterielle ion hydrogene CO_2 et anoxemie

It seems incorrect to regard section of the sino vagal nerves as a simple denervation o the chemoreceptors At the present time we are only beginning to explore the multiplicit of fibre components in the vagi—of those we know to date it would appear that th

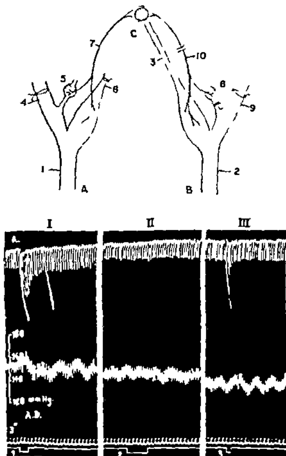


FIG 65*a* On the left side A the carotid innervation is intact On the right side B the sinus nerve is cut The internal and external carotid arteries are tied on the left (8 and 4) and the blood flow is directed to the carotid body (5) On the right the carotid body is excluded from the carotid circulation (6) and the external carotid artery is tied (9) Carotid blood is directed towards the res piratory centre C via the internal carotid (3)

FIG 65*b* Records from above downwards respiration blood pressure time in 3 second intervals and signal marker *I Injection of 1 ml sodium bicarbonate 3 per cent into the innervated carotid* A—hypernœa II Injection of 2 ml of the same solution into the vertebral artery—no effect III Injection of 0 1 ml sodium bicarbonate 3 per cent solution into the innervated carotid—hyperpnœa —(C Heymans J J Bouckaert and P Regniers (1933) *Le sinus caroti l en* Doin Paris)

receptors from the atrio caval junction from the pulmonary veins and the pulmonar arteries are discharging tonically All of these are capable of influencing the respiration In addition there are the Hering Breuer fibres from the lungs which influence ever discharge of the inspiratory centre Sino vagal section involves the baroreceptor fibre of the sino aortic area and as a result the mean blood pressure is perhaps 100 mm highe

than before This presumably increases the medullary blood flow considerably and sets new problems as to the equilibrium reached between the medullary pCO level and that of the cerebral venous blood The two conditions before and after sino vagotomy are sufficiently different to recommend caution in our statement which should simply be—the chemoreceptors are not necessary for the ventilation response of the animal to CO

Comroe & Schmidt (1938) studied the threshold of the central and chemoreflex responses to CO excess Dogs anæsthetized by morphine and chloralose were used The depressor nerves if identified were cut otherwise both vago depressor trunks were sectioned One carotid bifurcation was isolated A ligature was tied between the origin of the occipital artery and the carotid sinus The external carotid artery was ligated distal to the origin of the lingual artery The lingual artery was cannulated and the carotid body was perfused via the lingual and occipital arteries by means of a pump The carotid body was initially perfused with oxygenated Ringer Locke solution While the dog breathed oxygen about 200 ml of blood were removed from the femoral artery heparinized and stored under oil in a reservoir Then an inhalation of 10% CO in O was given and at the height of the hyperpnœa a second sample of 100 ml was collected under oil A third sample was withdrawn at the height of anoxic hyperpnœa induced by the inhalation of nitrogen If necessary the blood volume was made up by injections of fresh heparinized blood from another animal The blood samples removed were then successively perfused through the carotid body Their CO content and pH were determined Forty one observations were made of the systemic and reflex effects of hypercapnia on the breathing

To increased CO there was no reflex response in any of 8 cases below an increase of 4 vols % a response in half of 12 cases at an increase ranging from 4 to 8 vols % in 55% of 9 cases with increases between 8 and 12 vols % and in 77% of 9 cases over the range of 12 to 16 vols % It was only when the increase amounted to more than 16 vols % that the response was constant In all these experiments only one carotid body was perfused at a time During the systemic responses either one or both or neither carotid body might be functioning In a comparison of the reflex and systemic responses to CO they found that an increase of 2 vols % in the CO content of the systemic blood increased respiration 50% (average of seven experiments) an increase from 2–4 vols % practically doubled the ventilation volume but in none of these eight observations was the same blood adequate to stimulate the carotid body when perfused through it Reflex hyperpnœas were not seen constantly until the increase in CO amounted to more than 14 vols % The smallest rise in blood CO by which a reflex hyperpnœa was elicited was 4 7 vols % pH was reduced by 0 22 This represents an increase in CO tension of approximately 20 mm of mercury This last statement can hardly be correct The slope of the CO dissociation plotted for convenience as log content/log tension is given by the empirical equation (Peters *et al* 1924)

$$\Delta \text{ CO content}_{30\text{-}60} = 6\ 3 + 0\ 334\ h$$

where Δ CO content$_{30\text{-}60}$ is the increase in content caused by raising the tension from 30-60 mm pCO

and h is the oxygen capacity of the blood (vols %)

Assuming an oxygen capacity of 18 vols % we get

$$\Delta \text{ CO}_{30\ 60} = 6\ 3 + 6\ 0$$
$$= 12\ 3 \text{ vols } \%$$

So in the physiological range an increase of 4 7 vols % could not be equivalent to more than 10 mm rise in the pCO Below 30 mm pCO the slope of the graph is greater and therefore the increase in content represents a smaller change of tension Above 60 mm the slope remains the same up to 90 mm Hg (Nashat 1956) Secondly the pH change of 0 22 is altogether excessive for an increase in content of 4 7 vols % The change in pH could not have been greater than about 0 10 (see Brewin Gould Nashat & Neil 1955) The minimal reflex response therefore seems to be about twice as sensitive as the authors claim In a short subsequent note (1940) the authors admitted that the pH measurements were faulty There are however much more serious criticisms to be levelled at the interpretations of these experimental results The carotid body response to which the authors refer is assessed in terms of a respiratory response and is compared with the respiratory response which occurs when the animal inhales CO In systemic hypercapnia the respiratory mechanism increases its activity but the stimulus remains considerable The situation differs when one carotid body is stimulated by a local change in CO_2 tension and the afferent stimuli thereby aroused impinge on a centre which is not itself subjected to the hypercapnia Any increase in the respiratory response will reduce the centrogenic drive due to CO_2 and hence will tend to diminish the breathing The data presented by the authors are valuable in that they reveal that the centre is so sensitive to CO (or pH) that powerful chemoreceptor activity is required to drive the breathing but the results give no indication as to the sensitivity of the reflex mechanism when systemic *hypercapnia occurs The absence of stimulation of the breathing during local hypercapnia* of the chemoreceptor area may of course mean that the chemoreceptors are not stimulated but one cannot assume this as Comroe & Schmidt did

Evidence collected from other sources suggested that the chemoreceptors were not only tonically active themselves but contributed to the respiratory response to CO

Samaan & Stella (1935) found that chemo potentials were present above tensions of 32–35 mm CO in cats ventilated with air von Euler Liljestrand & Zotterman (1939) showed that chemoreceptor action potentials were present even in cats ventilated with oxygen providing that the arterial pCO was above 30 mm The impulse frequency increased linearly as the alveolar pCO was raised from about 35 mm Hg to 80 mm Hg Schmidt & Comroe (1940) expressed doubts as to the source of these impulses but as we have seen previously these can be safely set at rest On the other hand the mere presence of chemoreceptor activity does not mean that the respiratory centre is being driven by the chemoreceptor afferents The only way to show this is to block the chemoreceptor nerves and examine the effect on respiration There are three objections here (1) The preparation of the carotid bifurcations for blocking of the sinus nerves may affect the local glomus circulation The pressoreceptors must be inactivated or precautions must be taken to ensure that their activity is constant so that blocking of the sinus nerves causes effects solely referable to the removal of chemoreceptor stimulation (2) The aortic chemoreceptors cannot be easily inactivated themselves so that the vagi must be cut The mechanism of respiratory control is thereby altered by the section of the Hering Breuer afferents (3) After section of the vagi and inactivation of the carotid baroreceptors the level of arterial blood pressure and the cerebral blood flow may be far removed from normal

von Euler & Liljestrand (1940) showed that section of the sinus nerves was followed by a marked rise in resting alveolar pCO_2 which was due to depression of the breathing. The effect was lessened but was not abolished if the animals were breathing pure oxygen. They confirmed this in decerebrate as well as in anæsthetized dogs and cats. They concluded that the carbon dioxide tension of the blood under physiological conditions stimulates respiration not only by direct action on the respiratory centre but also reflexly over the sinus mechanism. The experimental technique employed entailed the simultaneous loss of the baroreceptor reflexes however (see also Stella 1935).

Schmidt Dumke & Dripps (1939) re-examined the problem in dogs lightly anæsthetized by morphine and chloralose. The vagi were cut and the carotid pressoreceptors were divided. Reactivity of the carotid chemoreceptors was tested by intracarotid injections of sodium cyanide. The animals breathed pure oxygen during the control period in which a blood sample was removed whereupon 1–2% CO_2/O_2 mixtures were substituted as the inhalant. An increase of 50 ml in the tidal volume lasting for two successive breaths was taken as an arbitrary criterion of hyperpnœa after which time a second blood sample was withdrawn and the CO_2 mixture was replaced by oxygen. Both carotid bodies were then infiltrated with procaine and thus inactivated as proved by the subsequent absence of response to intracarotid injections of cyanide. The procedure outlined was repeated. Blood samples were centrifuged and plasma CO_2 contents and pH values measured. The results were clear cut on inspection of the record shown in their paper. The response to 1 5% CO_2 in O_2 was not depressed and even occurred more briskly after chemoreceptor blockade. The average increase in (calculated) pCO_2 at which the hyperpnœa began was identical under the two conditions (3 3–3 4 mm Hg). The chemoreceptors did not aid the respiratory response to hypercapnia. However, the table presented which purports to show that inactivation of the chemoreceptors has no effect on the resting ventilation is much less convincing. In a series of eight dogs the average figures are given for pulmonary ventilation volume plasma CO_2 content pH and pCO_2 of the arterial blood before and after chemoreceptor inactivation —

	Pulmonary ventilation ml/min	CO_2 content Vols	pH	pCO_2 mm Hg
before	3 200	45 9	7 40	33 3
after	3,260	44 7	7 39	33 6

However on inspection the data from which these average figures were obtained reveal that the pulmonary ventilation volumes in this series ranged between 1 800 and 8 000 ml/min before and between 2 200 and 6 100 after chemoreceptor inactivation. Two of the dogs had (calculated) pCO_2 values of below 30 mm before the chemoreceptors were eliminated. One would not expect them to show any chemoreceptor drive. In many of the dogs we find that chemoreceptor denervation caused a greater change in plasma CO_2 content than in the CO_2 tension which is quite impossible from the very nature of the CO_2 dissociation curve of true plasma (e g dog 4 whose CO_2 content was 48 0 vols % and whose pCO_2 was 36 5 after chemoreceptor denervation showed a content of 42 7 vols % and a pCO_2 of 33 5. Dog 1 showed an alteration of breathing from 1 800 ml/min to 3 400 ml/min after chemoreceptor denervation but this apparently only lowered its pCO_2 from 28 4 mm Hg to 24 8 mm Hg). All that can be said therefore from their results is that the chemoreceptors did not respond more rapidly to an increase of CO_2 than did the centre in these dogs breathing oxygen.

Gesell Lapides & Levin (1940) introduced the sinus nerve cold block technique to evaluate the role of the chemoreceptors in hypercapnia Both carotid bifurcations were exposed in dogs ligatures were tied on the common carotid arteries below the carotid sinuses on the internal carotid arteries and on the external carotid arteries immediately rostral to the sinuses but caudal to the origin of the occipital arteries—the so-called Gollwitzer Meier ligature 6 (Gollwitzer Meier 1934) The carotid sinuses were then punctured The carotid bodies it was asserted obtained a satisfactory perfusion from anastomotic channels This may have been so but it is probable that their blood flow was less than normal Both vagi were cut The sinus nerves were dissected free from surrounding tissue and were placed on thermodes through which warm or cold solutions could be circulated as desired The dogs inhaled oxygen and the chemoreceptor con tribution to the breathing was evaluated by comparing the pulmonary ventilation volume before and after cold blocking the sinus nerves with that during cold block The respiration was reduced by blocking the nerves The dogs were then made to inhale mixtures of CO in oxygen and cold blocking of the sinus nerves was again used to see the effect of withdrawing the chemoreceptor impulses On CO /O mixtures up to a strength of 3 5% CO_2 in O blocking reduced the ventilation volume On a 6% CO /O mixture however the respiration was unchanged when the chemoreceptor afferent fibres were cooled Gesell and his co workers concluded that synaptic transmission of the chemo receptor impulses was blocked at high arterial pCO or pH levels They referred to Schmidt & Comroe s (1940) claim that the contribution of the chemoreceptors to the con trol of breathing increased as the level of CO tension rose They pointed out that no one had ever actually found this other than Schmidt & Comroe Their conclusion that block age of the synaptic transmission was the explanation of their findings was severely criticized by Schmidt & Comroe (1941) These authors now seemed to abandon their previous views and stated that Gesell s results might be taken to mean that CO is a strong stimulus to the centre but a relatively weak one to the chemoreceptors—a relatively feeble chemo receptor contribution to the respiratory response could thus be eliminated without its absence being noted in the presence of overpoweringly strong central stimulation There is no question however that the impulse activity from the chemoreceptors progressively increases as the CO tension in the blood rises (Euler *et al* 1939 Bartels & Witzleb 1956) Cooling the sinus nerves during the inhalation of 3% CO /O by the dogs caused an obvious reduction in the ventilation volume in Gesell s experiments Therefore cooling the sinus nerves during the inhalation of 6 / CO_2/O should cause a still more obvious reduction in the ventilation volume unless the chemoreceptor afferent impulses were no longer stimulating the respiratory neurones Schmidt & Comroe have not in any way explained Gesell s finding—they merely put his answer in different words and thereby altered the sense Whatever the explanation may be the practical point remains the same—that in pure hypercapnia the respiratory activity is due to the central effects of CO entirely—as Gesell said the hyperpnœa is centrogenic

Hesser (1949) extended these observations The carotid sinus pressoreceptor fibres were cut so that blocking of the sinus nerves by cold thermodes caused effects due to the interruption of the chemoreceptor impulses only The cerebral circulation and local sinus circulation was normal The vagi were cut and the procedure employed was similar to that of Gesell *et al* Simultaneous photographic recordings were made of pulmonary

ventilation arterial pH alveolar pCO arterial O saturation and arterial blood pressure Even during the inhalation of pure oxygen blocking the sinus nerves caused a small but definite reduction of respiration which indicated that the chemoreflex mechanism had a tonic influence on the respiratory activity The centre alone was unable to maintain the pCO at the usual level (see Figure 10 of Hesser 1949) In experiments in which the animals rebreathed from a spirometer containing oxygen it was found that cold block of the sinus nerves caused no effect on the breathing when the alveolar pCO exceeded 60 mm Hg Hesser concluded that the chemoreflexes had only a minor share in the hyperpnœa of low grade hypercapnia and that they did not support the hyperpnœa of marked hypercapnia at all He agreed that the outcome of the chemoreflex impulses (i e the chemoreceptor drive) was influenced by a modifying action of the arterial cH at the centre or along the chemoreflex nerve pathway Hesser also stressed that as long as the stimulation of the chemosensitive cells in the chemoreceptors and centre is not caused by chemical changes in the arterial blood acting on both structures the condition is not only artificial but will derange the normal interaction of the two components —a most important point Gollwitzer Meier & Lerche (1940) also compared central and reflex respiratory responses to changes of arterial pCO and found the threshold change for a reflex respiratory response to be 6 mm pCO —a rise from 31 to 37 mm Hg corresponding to a pH decrease of 0 055 They pointed out that the centre was more sensitive still and therefore disagreed with Heymans & Bouckaert (1939) but also disagreed with Comroe & Schmidt s view that the chemoreceptors responded only to great changes of CO tension

Lastly Bartels & Witzleb (1956) have recently re examined the response of the chemo receptors themselves to changes of CO in the blood Cats anæsthetized by chloralose and urethane were ventilated by a Starling pump with mixtures of 30–32% O in N and 3 2 9 9 and 12 7% CO_2 in 30–32% O_2 in N Changes of arterial CO tension from 25–120 mm Hg were produced thereby There was a linear relationship between the CO tension and the chemoreceptor impulse activity There was also a linear relationship between the pH and the chemoreceptor impulse activity The threshold CO_2 tension at which the chemoreceptor impulses began was under 30 mm Hg They preferred not to comment on the implications of their findings with respect to the control of respiration

In summary we can say that there is ample evidence that the chemoreceptors are tonically active in response to the CO tension of the blood in eupnœic conditions in the anæsthetized animal (von Euler *et al* Bartels & Witzleb) Blocking the chemoreceptors causes a slight but definite decrease in the breathing even in animals breathing oxygen In animals breathing CO/O mixtures chemoreceptor blockade still causes a reduction in pulmonary ventilation providing that the CO content of the inspired gas mixture does not exceed 3 5% (Gesell Lapides & Levin) When the inspired gas contains more than 3 5% CO there is evidence that chemoreceptor blockade no longer influences the respiratory response The chemoreceptor impulses which are undoubtedly produced in such circumstances no longer stimulate the central respiratory mechanism Attempts to measure the threshold of chemoreceptor response by perfusing the glomus separately and measuring pulmonary ventilation have yielded misleading results

Even when the chemoreceptors have been inactivated the systemic response to CO remains almost unchanged The chemoreceptors are not essential to the respiratory

response to CO The question remains open as to how much they participate in the response to moderate hypercapnia in the intact animal

Meanwhile it seems wrong to assume that the effects of CO are entirely centrogenic De Castro (1951) has stated that hypercapnia causes an obvious change in the local circulation of the glomus so that a much greater volume of blood is by passed via the a–v shunts The implications of such findings are as yet not understood but it would be wise not to ignore the findings themselves

Anoxia

The chemoreflex response to anoxia is of vital importance to the organism unlike that to excess carbon dioxide After chemoreceptor denervation anoxia causes only depression of the breathing (Heymans *et al* 1931 1933) The arguments which still continue relate rather to the threshold and sensitivity of the chemoreflex respiratory response to acute anoxia In addition there is considerable discussion about the part played by the chemoreceptors in chronic anoxia

Comroe & Schmidt (1938) first announced the chemoreceptor threshold to a lowered arterial pO to be about 50 mm Hg Bernthal (1944) commented The reasons for the low sensitivity can only be guessed They are however immaterial for again the threshold was determined by perfusing blood of low oxygen content through the glomus and noting the respiratory response and the objections to this technique have already been detailed in the previous section

von Euler Liljestrand & Zotterman (1939) showed by recording action potentials in the sinus nerve that the chemoreceptor threshold lay above 100 mm Hg pO This has lately been confirmed by Witzleb Bartels Budde & Mochizucki (1955) Naturally this is the threshold of some of the receptors only When anoxia is induced besides increased impulse frequency in individual afferent fibres there is a recruitment of other units Such then is the threshold of the chemoreceptors Much more important however is the threshold of the chemoreceptor effect on the breathing Gesell Lapides & Levin (1940) showed that blockade of the carotid chemoreceptor afferents (by cooling them) caused a definite reduction of the pulmonary ventilation of vagotomized dogs breathing air (Selladurai & Wright 1932) Euler & Liljestrand (1936) found that section of the sinus nerves lowered the ventilation volume The same criticism may be levelled at each of these results The preparation entailed in each case is such as would be likely to cause some slowing of the glomus circulation This would favour a resting chemoreceptor discharge and a chemoreflex respiratory response

The only alternative to such experiments is to assume that the inhalation of oxygen will exert an effect on the breathing solely due to the withdrawal of tonic chemoreceptor activity caused by the level of arterial pO (Euler & Liljestrand 1940 1942) The quantitative difference in the breathing caused by substituting oxygen for air as the inhalant can then be taken as a measure of the tonic chemoreceptor drive due to chemo receptor anoxia Needless to say it cannot give any evidence as to the tonic chemoreceptor drive due to arterial pCO_2 The animal need not be subjected to any trauma a cuffed endotracheal tube can be inserted via the mouth The tube is then connected to respira tory valves and after a steady state has been observed on air oxygen is substituted as the inspired gas The respiration is invariably reduced but the maximal reduction is not

maintained The pulmonary ventilation volume shows a secondary restoration towards its original level This secondary restoration is less obvious if 30% O is used rather than 100% O The reasons for the secondary rise may be

(1) hypopnœa due to the removal of anoxic chemoreceptor drive causes a rise in the alveolar CO This stimulates both the respiratory chemocentre neurones and the chemoreceptors themselves and thereby increases the breathing
(2) Cerebral vasoconstriction (Kety & Schmidt 1948) caused by the inhalation of 100% O may cause a rise in the pCO of venous blood leaving the medullary chemocentre (Lambertsen *et al* 1953*a*) According to Lambertsen and his colleagues (1953*a* *b*) the cerebral venous pCO is that most closely related to the intracellular pCO of the respiratory neurones

When air is substituted again for oxygen the breathing again shows a transient increase If one assumes then that 30% O exerts its effect on the breathing solely by abolishing tonic anoxic drive from the chemoreceptors these results are in harmony with the belief that such a drive exists in the anæsthetized animal

The same results are obtained in unanæsthetized man Loeshke (1953) found that the ventilation volume was reduced by 8% when 32% O in N was substituted for room air This decrease was only seen for about a minute and was later superseded by a second ary increase in the breathing until after about four minutes a new equilibrium was reached On restoring room air as the inspired gas mixture the ventilation volume again increased and remained raised for some twelve minutes During this time CO which had accumulated was eliminated Loeshke concluded that there was a normal chemoreceptor drive aroused by the arterial pO level which exists in eupnœic breathing Dripps & Comroe (1947) also were able to show a very slight reduction (3 1%) in the pulmonary ventilation volume caused by the inhalation of 100% O Cross & Warner (1951) found that the same procedure—the substitution of pure oxygen for air as the inhalant—caused a rather greater percentage reduction of the ventilation volume of new born babies In both cases the initial hypopnœa was superseded within a minute or so by a slight hyperpnœa This was perhaps due to (*a*) increase of arterial pCO due to the early hypopnœa (*b*) increase of venous pCO in the vicinity of the respiratory centre due to cerebral vasoconstriction caused by the high oxygen tension Kety & Schmidt (1948) showed that the blood flow through the brain fell from 54 ml /100g /min to 45 ml /100g /min when their subjects breathed oxygen instead of air The results of Dripps & Comroe and Cross & Warner proved that there is a slight reduction of breathing only detectable if the measurements are made with scrupulous care when the arterial pO_2 is raised from 100 mm Hg to higher levels

When one examines the respiratory response to oxygen tensions lower than that of room air at ground level however nearly all the data obtained corroborate the findings of Haldane & Lorrain Smith that the breathing shows no increase until the inspired pO falls below 100 mm Hg (Boycott & Haldane 1908, Rahn & Otis 1949) Dripps & Comroe (1947) made a very careful study of this in a large series of subjects They pointed out that Ellis (1919) and Lutz & Schneider (1919) had reported that the inhalation of 18% O in N caused some hyperpnœa in some of their subjects whereas Boothby (1945) had found that no change in respiration occurred until 16% O in N was breathed Dripps & Comroe noted that psychic factors and individual variations in the response played a

noticeable part in these earlier series and made every attempt to standardize their pro cedure In fourteen of their subjects exposed to 18% O in N eight showed a slight decrease in ventilation and six a slight increase Seventeen out of twenty subjects showed an increase of about 0 5 l/min in their pulmonary ventilation when breathing 16% O in N Eight out of ten subjects increased their breathing by 0 5 l/min breathing 14 5% O in N It was not until 10% O in N_2 was inhaled that all the subjects tested increased their pulmonary ventilation by an average of 1 3 l/min (range 0 6–6 3 l/min)

Further studies showed that the inhalation of 8% O in N caused an average increase of 6 l/min (range 1 7 to 12 9 l/min)

Horvath Dill & Corwin (1943) studied the respiratory response of schizophrenic patients to very low oxygen mixtures The patients were subjected to these mixtures for periods ranging from ten to fifteen minutes either up to the point of unconsciousness or in some cases extending into unconsciousness On 4 2% oxygen in nitrogen the pulmonary ventilation volume reached an average of 30 litres per minute A striking feature was the wide range in the respiratory minute volumes reached by the various subjects This is a characteristic of the response of healthy men to anoxia and accounts for the variability in their altitude ceiling Following the anoxic period the breathing slowly returned to normal As Horvath *et al* point out it is usually taught that a period of overventilation is followed by a period of apnœa or hypopnœa but this was not the case with these patients (see also results of Davenport *et al* on dogs (1947)) 4 2% oxygen is equivalent physiologically to an altitude of about 31 000 feet This must be about the ceiling of unacclimatized man when one remembers the fate of Croce Spinelli and Sivel in the balloon ascent of 1875 described by the only survivor Tissandier (Paul Bert 1878) The balloon reached 30 000 ft (B=263 mm Hg)

The hyperpnœa caused by anoxia induces acapnia and alkalosis Haldane and others recognized that anoxia would be a much more powerful stimulus to the breathing if the acapnia could be prevented Gray (1945–1950) has stated that anoxia alone can cause only an increase of 65% in the breathing He has calculated that the same anoxic stimulus can increase the breathing by 700 % if the alveolar CO tension is maintained at its normal level The assumption made in his calculations is that anoxia and hyper capnia exert simply additive effects on the breathing This assumption which seems unlikely is refuted by recent evidence from two sources

(*a*) Nielsen & Smith (1951) exposed two subjects to low oxygen tensions such as produced alveolar oxygen tensions of 37–39 mm Hg Their ventilation volume was 18 litres per minute and their alveolar CO tension was about 21 mm Hg The alveolar CO tension was then raised by adding CO_2 to the inspired gas mixture and the oxygen content of the mixture was meanwhile adjusted to maintain a constant alveolar oxygen tension The breathing was unaffected until the alveolar carbon dioxide tension was thus artificially raised to 30–33 mm Hg—a value which the authors refer to as the threshold or apnœa point With further increases in the alveolar pCO the ventilation volume increased linearly (Fig 66) The slope obtained by plotting the ventilation volume against the alveolar CO tension was greater in acute anoxia than when the subjects breathed similar CO mixtures made up in room air Nielsen and Smith concluded that the sensitivity of the respiratory mechanism was greater during acute anoxia than during air breathing This increased sensitivity to carbon dioxide plays no part in contributing to

the hyperpnœa of acute anoxia because the alveolar pCO is far below the threshold value The authors suggested that it may have biological importance in asphyxia when anoxia and hypercarbia occur simultaneously These results do not support Gray s supposition that anoxia and hypercapnia act additively

(*b*) Cormack Cunningham & Gee (1955) exposed subjects to progressive anoxia and maintained the alveolar pCO constant Plotting the ventilation volume against the

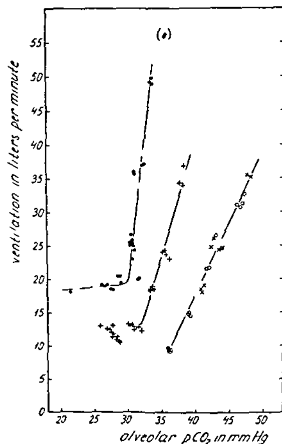


Fig 66 Man Subject P G pulmonary ventilation (37 prevailing bar pressure saturat) in relation to alveolar pCO
● Alveolar pO_2 36 9 ± 1 3 mm Hg
\+ 47 2 ± 1 5
o 110 3 ± 1 9
x 168 7 ± 2 1
(M Nielsen and H Smith (1951) *Acta physiol scand* 24 293)

alveolar pO they found that their experimental points lay below the curve calculated by Gray Their experimental values agreed well on the other hand with those calculated from the alveolar gas tensions published by Miss Fitzgerald (1913) from her study of subjects acclimatized to various degrees of anoxia They regard Miss Fitzgerald s figures as typifying the respiratory response to anoxia of subjects who were free from acapnia If acapnia (smokelessness —Mosso 1898) is taken to mean the symptoms resulting from lowering the alveolar CO tension this is a reasonable statement The interesting point is that their ventilation volume/pCO graph in acute anoxia should agree with that of acclimatized man As will be seen later it is now argued that the respiration in acclimatized subjects is governed mainly by the CO_2/HCO_3 ratio irrespective of the

alveolar oxygen tension This argument must be affected however by these findings of Cormack *et al* in subjects where the sole stimulus to breathing was anoxia

Cormack *et al* (1955) also investigated the respiratory response to anoxia when the alveolar CO tension was kept constant at either 5 mm or 10 mm Hg above normal In four of the five subjects the increments in ventilatory response to successive grades of oxygen lack were much greater at the higher levels of alveolar CO_2 tension Their results strongly suggest that there is a positive interaction between anoxia and hypercapnia and further studies by the same authors (Cormack *et al* 1956 1957) confirm this

Chapter 18

THE RESPIRATORY RESPONSE TO CHRONIC ANOXIA AND EXERCISE

Chronic Anoxia

Rahn & Otis (1949) studied the respiratory response of unanæsthetized men to acute and chronic anoxia at an altitude of 9 500 ft (B = 535 mm Hg). No change was detected in the alveolar pCO_2 during acute exposure and it was inferred that no hyperpnœa had developed. Three subjects were allowed to acclimatize to this degree of anoxia and their alveolar CO_2 tension fell to reach a final value in four days; 50% of the total reduction

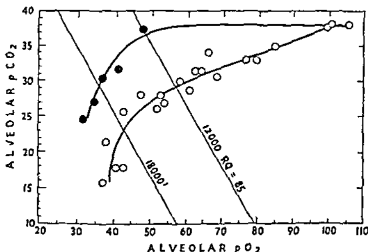


Fig. 67. Differences in alveolar gas composition between man acutely exposed to various altitudes (solid circles) and man acclimatized to various altitudes (open circles).—(H. Rahn and A. B. Otis (1949) *Amer. J. Physiol.* 157, 145)

in the alveolar CO_2 tension was effected in twelve hours (see also D'Angelo, 1946). Fig. 67 from their paper summarizes the respiratory response to anoxia on the part of unacclimatized and acclimatized subjects respectively. Clearly the acclimatized subject responds to even slight anoxia by overbreathing, whereas the non-acclimatized person shows no fall in alveolar CO_2 tension and therefore no hyperpnœa until the alveolar pO_2 falls below 60 mm Hg. The authors consider that the chemoreceptor activity aroused by moderate anoxia is offset by the accompanying inhibition of the respiratory centre caused by alkalosis due to the desaturation of the hæmoglobin in the

arterial blood At an arterial oxygen tension of 50 mm Hg and a CO tension of 38 mm Hg the % saturation of hæmoglobin would be 86 This desaturation would theoretically increase the plasma pH by 0 008 On the basis of Gray s multiple factor theory this degree of alkalosis would produce an inhibition of about 16% of the ventilation which would offset the anoxic drive of 20% (calculated from the same theory) The author of the theoretical treatment denies this (Gray & Grodins 1951) and draws attention to his own analysis of the same data Gray considers that the phenomenon of hyperpnœa in acclimatized moderate anoxia is due to an increased sensitivity of the respiratory mechan ism to CO as do Asmussen & Nielsen (1953) Rahn & Otis claim on the other hand that the chemoreceptors cannot affect the respiratory centre until the kidney has compensated for this desaturation alkalosis by excreting base

Berger *et al* (1949) found an increase of sodium excretion in men breathing 14% O Axelrod & Pitts (1952) noted that there was occasionally an increased sodium excretion in dogs breathing 6 3% O as there were no changes in Tm_G and Tm_{PAH} they concluded as did Berger *et al* that the changes in sodium excretion were not due to effects of hypoxia on the tubular mechanism itself but rather to extra renal causes Selkurt (1953) however has proved that pump perfused kidneys increase their urinary output of sodium when per fused with hypoxic blood Moreover McDonald & Kelly (1948) have claimed that glucose Tm_G is reduced in moderate hypoxia Whereas kidney tissue normally operates at a higher tissue pO_2 than most organs (Van Slyke *et al* 1934) it seems unlikely from the above evidence that acute moderate hypoxia can exert any direct influence on the renal tubular handling of sodium or bicarbonate More evidence is required as to the effects of hypoxia in altering the excretion of mineralocorticoids (see Thorn *et al* 1945) before we can assess the role of the kidney in causing acid base changes in the initial stages of hypoxia As Christensen (1954) admits how the acclimatization process is initiated we do not know

With a severity of anoxia which induces hyperpnœa even when the subject is acutely exposed the problem is simpler The immediate reduction of the alveolar pCO causes respiratory alkalosis and in turn provides a known stimulus to the renal excretory mechanisms The adjustment of the arterial pH to more normal values by the excretion of bicarbonate is widely documented but the studies of Dill Talbott & Consolazio (1937) remain the most complete Acclimatized dwellers at an altitude of 5 34 km showed one major change in the electrolyte pattern of their plasma—a loss of bicarbonate which might be as much as 8 milliequivalents below sea level values This was compensated for by an increase in chloride of 4 mEq /L and a sodium decrease of 2 mEq /L leaving an unexplained anion deficit of about 2 mEq /L

As a result of chronic exposure to oxygen lack the breathing reaches a greater minute volume than during acute anoxia The process of respiratory acclimatization requires about 7–10 days at an altitude of 14 000 feet (Douglas *et al* 1913 See also Houston & Riley (1947) for data on partial acclimatization at altitudes up to 22 000 feet)

Once acclimatization has been established the respiration shows little change when the inspired oxygen tension is suddenly raised This is in harmony with the experience of high altitude mountaineers who having acclimatized find that their hyperpnœa persists for several days on their returning to the plains Such evidence suggests that the anoxic stimulus is not of much importance in the control of the breathing in acclimatized subjects Rahn & Otis (1949) strongly supported the opinion that the respiratory control in the

acclimatized subject was once more exercised by changes in the CO /HCO_3 ratio They accepted the results of animal studies by Bjurstedt (1946) as supporting this hypothesis Bjurstedt examined the effect of sudden increases in the inspired oxygen tension on the *breathing of anæsthetized dogs exposed to long periods of severe anoxia In technically* beautiful experiments he measured simultaneously the arterial pH arterial oxygen

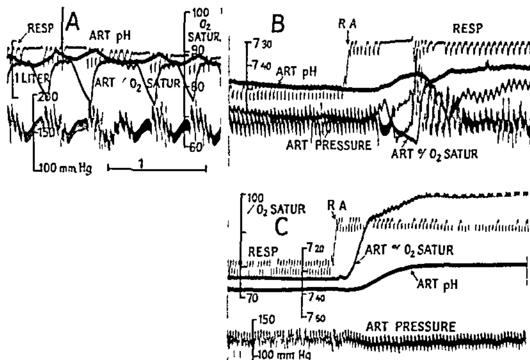


FIG 68 Dog Effects of a sudden increase in the oxygen supply during hypoxic hyperventilation at the stage of maximum respiratory alkalosis (B) and after the compensation of the alkalosis has become nearly complete (C) The calibrations in A and B apply to both figures
A Periodic breathing in room air
B After breathing of 8 2 per cent O_2 in N_2 for 15 minutes At R A sudden supply to the spirometer of O_2 so that its O_2 content became rapidly the same as in room air Note in. ufficiency of breathing and the first apnea
C After 8 hours breathing of 8 2 per cent O in N The respiratory alkalosis was now nearly compensated R A = see B Note the rapid and great increase in the arterial O_2 saturation compared to B —(A G H Bjurstedt (1946) *Acta physiol scand* 12 Suppl 38)

saturation pulmonary ventilation volume and blood pressure The dogs breathed 8 2% oxygen in nitrogen which induced hyperpnœa and respiratory alkalosis—the plasma pH rose from 7 35 to 7 50 After 15 minutes the temporary substitution of room air as the inhalant caused an obvious reduction in the breathing However after eight hours inhalation of the low oxygen mixture the substitution of room air caused a smaller reduction of the pulmonary ventilation (Fig 68) During this period of anoxia the plasma pH had gradually returned towards a more normal value Bjurstedt asserted but did not

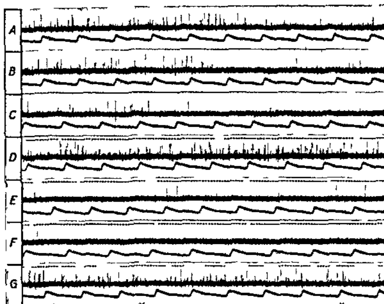


FIG 69

Record	Simulated altitude	Tracheal pO mm Hg	Pulmonary ventilation l/minute	Number of spikes
A	4 000 m	87	0 847	93
B	Sea level instantly	149		50
C	Sea level 4 minutes later	149	0 664	24
D	6 000 m	68	0 974	139
E	Oxygen instantly	415		11
F	Oxygen 4 minutes later	415	0 705	1
G	4 000 m	87	0 861	90

Cat 2 8 kg chloralose—urethane anæsthesia Spontaneous respiration Right carotid sinus nerve cut centrally baroceptor fibres removed by dissection Right femoral artery cannulated for recording blood pressure A cannula was inserted into the trachea for measurements of the pulmonary ventilation Records on each film strip from above downwards time (50 c/s) electro neurogram and arterial blood pressure Blood pressure calibration lines show 150 and 100 mm Hg The times when these records were taken are shown in the table (letter A to G) The records show the chemoceptor activity after acclimatization to simulated altitude (4 000 m) for 64 hours when breathing air (4 000 m) oxygen and gas mixtures giving a tracheal oxygen pressure corresponding to 6 000 m and sea level Note the reduction of the chemoceptor activity and pulmonary ventilation when the oxygen tension of the inspired air was increased (C and F) —(P O Åstrand (1954) *Acta physiol scand* 30 335)

confirm that this restoration of the plasma pH was due to renal compensatory mechanisms He concluded that the small effect of raising the oxygen tension on the breathing was due to the restoration of the CO /HCO_3 ratio The figure shown however reveals that the reduction in the breathing caused by rai ing the inspired oxygen tension after eight hours of anoxia was still sufficient to lower the arterial pH by 0 13 It is fair

to say that the example given is less persuasive than the argument which is built round it In any case it seems unwise to draw conclusions from quantitative responses obtained from an animal before and after eight hours exposure on an operating table Rahn & Otis however raised no such objections in accepting these data They themselves had shown that the respiratory response of acclimatized unanæsthetized man to inspired CO mixtures was greater than that at ground level Moreover the breath holding time of an acclimatized subject was shorter than that of the same subject exposed acutely to the same altitude (Schneider 1931) Both these findings they reasonably ascribed to the lower alkali reserve of the acclimatized person Neither of these results however gives much information as to the control of breathing in chronic anoxia

Åstrand (1954) investigated the effects of chronic anoxia on the activity of the chemoreceptors themselves as sampled by the electroneurogram Unanæsthetized cats were exposed in a low pressure chamber for periods of 13–64 hours to a simulated altitude of 4 000 metres (tracheal pO =87 mm Hg) At the end of this period the cat was anæsthetized the trachea was cannulated and one carotid sinus nerve was cut centrally A chemoreceptor fibre preparation was made and the electroneurogram was recorded The tracheal cannula was connected to inspiratory and expiratory water valves Suitable gas mixtures were administered via the inspiratory valves A spirometer recording on a kymograph collected the expired air The results obtained in a cat anæsthetized after 64 hours in the low pressure chamber are shown in Figure 69 At the 4 000 m altitude breathing room air the pulmonary ventilation was 0 847 l /min and there was a steady discharge of chemoreceptor impulses The chemoreceptor activity was quickly dispelled by raising the pO_2 from 87 to 149 The pulmonary ventilation was also obviously reduced Conversely the chemoreceptor activity and pulmonary ventilation were both increased by lowering the pressure in the chamber to that of an altitude of 6 000 m (pO =68) There was thus no doubt that the chemoreceptors remained sensitive to acute reductions of arterial pO_2 (despite the chronic anoxia to which they had been subjected) and that the respiratory mechanism remained responsive to the increase in chemoreceptor traffic thus induced Åstrand discussed the disparity between his results and those of Bjurstedt It is possible of course that a species difference exists between cats and dogs Nevertheless as far as the cat is concerned Åstrand has advanced the most important evidence yet presented as to the behaviour of the chemoreceptors *themselves* in chronic anoxia chloralose anæsthesia has no effect on the peripheral mechanism of these receptors (as can be easily seen by testing the effect of adding suitable amounts of chloralose to the fluid perfusing the carotid body and checking the electroneurogram) The effect of this chemo receptor impulse traffic on the medullary respiratory centres probably is modified by the chloralose anæsthesia Hence the effect on respiration which the chemoreceptor traffic exerts may be exaggerated As Åstrand pointed out Bjurstedt s results obtained on anæsthetized dogs have been extrapolated to human problems by Rahn & Otis (1949) and Riley & Houston (1951) It is however necessary to stress that the results of the present paper as those of Bjurstedt were obtained on anæsthetized animals and cannot necessarily be extended *in toto* to conditions in the human unanæsthetized subject

In view of this careful statement it is somewhat surprising to find Rahn (1955) commenting that observed changes in action potential frequency of the carotid body nerves in anæsthetized hypoxic cats (Åstrand) are certainly no guarantee for an equivalent

change in the alveolar ventilation in unanæsthetized man It is well appreciated from the older literature that increased or decreased receptor activity is not necessarily synonymous with increased or decreased alveolar ventilation under these conditions and we must differentiate between chemoreflex drive and chemoreceptor activity Apart from his change of front his meaning is obscure There have been no previous studies of chemo receptor activity (measured directly) and alveolar ventilation Even if there had been the statement is irrelevant for Åstrand showed that the change in chemoreceptor activity was accompanied by a change in alveolar (or pulmonary) ventilation It is interesting to speculate as to how we can possibly differentiate between chemoreceptor activity and chemoreceptor drive except in an anæsthetized animal

Beard Bell & Howell (1953) exposed dogs for 7–15 weeks to a simulated altitude of 20 000 feet (P =350) in a low pressure chamber The animals were then returned to ground level for an hour after which they were anæsthetized to test their pulmonary vascular and ventilation response to 8 5% O in N which afforded the same inspired pO as that to which they were subjected at altitude The total ventilation increased approximately 50%

It seems therefore that acclimatization in the cat and the dog does not render the respiratory mechanism unresponsive to impulses from the chemoreceptors aroused by the state of anoxia But the experiments in which chemoreceptor activity and ventilation response are simultaneously assessed can only be performed in the anæsthetized animal and it is likely that the anæsthetic itself exaggerates the effect of chemoreceptor discharge on the respiratory mechanism Åstrand (1954) in an accompanying paper showed that the breathing in chronic anoxia (man) though scarcely affected by a rise in the inspired oxygen tension when the subject was at rest was obviously reduced when the subject was engaged in moderate exercise He argued that the study of respiratory control during chronic anoxia could be more profitably carried out against a background of moderate physical activity in view of the greater reproducibility of the respiratory minute volumes in such circumstances compared with that in the subject at rest

Rahn & Otis (1949) pointed out that their supposition that the respiratory responses of an acclimatized man were essentially controlled by the CO /HCO_3 ratio in the plasma could be tested by comparing these responses with those obtained in subjects in whom a depletion of the alkali reserve had been achieved by other means Two possibilities were suggested —(*a*) subjects continuously hyperventilated for long periods in whom renal compensatory changes for the respiratory alkalosis caused lowering of the alkali reserve and (*b*) subjects treated with ammonium chloride Brown Campbell Johnson Heming way & Visscher (1948) noted that there was a considerable increase in the sensitivity to carbon dioxide mixtures in subjects artificially hyperventilated for 24 hours Brown (1950) later claimed that the brain tissue of guinea pigs hyperventilated for 24 hours when ground up and made into 10% solution showed a slightly greater hydrogen ion concentration when exposed to a given CO_2 tension than did normal brain tissue similarly treated This is not surprising The graph shown in his paper reveals no difference of sensitivity to CO of the two solutions—the slope of the H^+/pCO line is the same in each case

The ingestion of ammonium chloride (15 g /day for three days) was declared to affect the breath holding time and the alveolar pCO at the breaking point in a manner similar to that observed after acclimatization to altitude by Rahn & Otis as a result of preliminary

experiments Presumably the experiments referred to are those of Stroud published later (1953) Stroud lowered the alkali reserve by about 20% in six men and reduced the arterial pH from 7 39 to 7 33 despite a fall in the alveolar pCO_2 from 38 7 to 31 6 mm Hg by administering ammonium chloride The breath holding time on air or oxygen was diminished there was a change in the CO threshold of the breaking point but there was no alteration in the sensitivity to CO as measured by the difference between the breaking point alveolar pCO and the resting alveolar pCO Stroud concluded that in altitude acclimatization the increased sensitivity to CO as tested by breath holding or by the response of the respiration to CO mixtures was not to be sought in the reduction of buffering capacity but was due to a sensitization to CO *per se* as claimed by Nielsen & Smith (1951) Rahn Bahnson Muxworthy & Hagen (1953) extended their observations on acclimatization and found that after seven days at 14 100 feet the breath holding time was reduced to 14 seconds on air compared with 25 seconds when the same subject was exposed acutely to this altitude They confirmed that the sensitivity of the respiratory mechanism to CO_2 was greatly increased—i e that a much smaller increment of alveolar pCO *was required before the breaking point of breath holding was reached* They therefore changed their original opinion in view of Stroud s results and supported Nielsen & Smith and Gray in claiming that the sensitivity of the breathing to CO is increased by oxygen lack Nielsen (1936) had shown that at normal oxygen pressures long lasting (12–16 days) decrease in the alkali reserve caused by the ingestion of ammonium chloride had only small effects on the breathing and as a result the arterial blood remained much more acid than normal This led to his discarding the supposition that chronic anoxic hyperpnœa was in any large measure due to lowering of the alkali reserve

Unfortunately this new found harmony seems destined to be short lived Winterstein & Gokhan (1953) have shown that the effects of ammonium chloride on the breathing cannot be simply referred to effects on the alkali reserve In addition the results of Fowler (1954) and his colleagues reveal that the breaking point of breath holding cannot be identified simply with a chemical stimulus Lastly, if one allows the opinion that there is an increase in the sensitivity of the respiratory mechanism to carbon dioxide Winterstein (1956) points out that this says nothing new It provides no explanation of the experimental observation that CO causes a greater respiratory response during anoxia acute or chronic than normally

It is perhaps worthwhile reflecting that a study of the changes in the electrolyte pattern of the cerebrospinal fluid might provide some of the clues to a solution of the puzzle The c s f contains no protein and is a poorly buffered solution—its titration curve is similar to that of bicarbonate solution A change of pCO must affect the pH of the c s f more profoundly than that of the plasma If one assumes that the pH of the c s f is of importance in determining respiratory activity as the results of Winterstein & Gokhan suggest then the initiation of anoxic hyperpnœa must cause a secondary inhibition of the breathing by producing alkalosis in the cerebrospinal fluid The slow rate of turnover of the constituents of the fluid may thus limit the speed of removal of this source of respiratory inhibition If the reduction in alkali reserve of the plasma in acclimatized man is reflected in the c s f then the fluid must be very poorly buffered indeed so that changes of CO_2 tension will cause considerable alterations in the pH This would account for the increased sensitivity of the breathing to CO in chronic anoxia It must be remembered that in

fully acclimatized men the buffer value of the blood is increased not decreased (as Dill *et al* showed) the increase in hæmoglobin concentration due to polycythæmia allows the blood to buffer the carbon dioxide more efficiently Thus the pH change in the respiratory cycle is one fourth less than normal The decrease in the alkaline reserve reduces the capacity of the body to deal with fixed acids It is possible therefore that the apparent dominance of centrogenic breathing in man when acclimatized to anoxia is to be related rather to the lowered bicarbonate content of the c s f than to that of the plasma On removing the anoxic stimulus suddenly the breathing may be little affected because the slightest rise of the CO tension caused by withdrawal of such chemoreceptor drive as might exist causes an immediate increase in the [H^+] of the c s f which stimulates the central neurones

The problem of hyperpnœa in chronic anoxia is not yet solved Such direct evidence as we possess points to there being maintained chemoreceptor discharge from the glomus nerve endings Indirect evidence leads us to suppose that the impulses aroused by anoxia do not effectively modify the breathing in chronic acclimatized oxygen lack Naturally the greater the hyperpnœic response which the chemoreceptors are able to produce in the initial stages of anoxia the smaller will be the chemoreceptor stimulus as a result for the arterial pO rises and the arterial pCO falls owing to the hyperventilation Nevertheless the reflex response cannot exceed the stimulus which causes it so that some anoxic chemo receptor discharge continues With the gradual restoration of arterial pH and c s f pH by the renal compensatory mechanism the anoxic chemoreceptor impulses apparently exert a diminishing effect on the central neurones We have no evidence as to whether the chemoreceptors contribute to the respiratory drive after acclimatization is complete by virtue of their response to the arterial pH

Man in Exercise

If the respiratory minute volume in the steady state during exercise of varying grades of severity is plotted against the oxygen usage per minute the relationship is linear at least up to oxygen usages of about 2¼ litres per minute The slope of the line depends on the efficiency with which the exercise is performed (Christensen 1937*a* Dickinson 1929 Schneider 1931 Taylor 1941) The only known way in which oxygen deficiency can be signalled to the respiratory neurones is by the chemoreceptors which respond to a fall of tension in the arterial blood At first sight it might seem remarkable that there should be a fall of arterial pO in a man breathing say 60 litres per minute However the blood arrives in the pulmonary capillaries at a much lower oxygen tension than normally and passes through them more quickly According to Roughton s (1954) calculations the blood spends 0 75 seconds in the pulmonary capillaries in the resting subject and only 0 33 seconds during heavy exercise Bannister (1956) refers to the recent work of Lee & DuBois (1955) which shows that the blood flow in the pulmonary capillaries is pulsatile and discusses how this may influence the equilibration with oxygen The only direct measurements so far made show that the arterial pO does fall—from 94 mm to 73 mm during three experiments on one subject working at moderate intensity (Lilienthal Riley Proemmel & Franke 1946) Such a fall would not cause any stimulation of the respiration of a subject at rest but the respiratory conditions in man during exercise are obviously different

If the exercising subject breathes 100% oxygen his pulmonary ventilation is considerably reduced (Nielsen & Hansen 1937 Asmussen & Nielsen 1946) Bannister & Cunningham (1954) showed that although 33% O reduced the respiration of a given

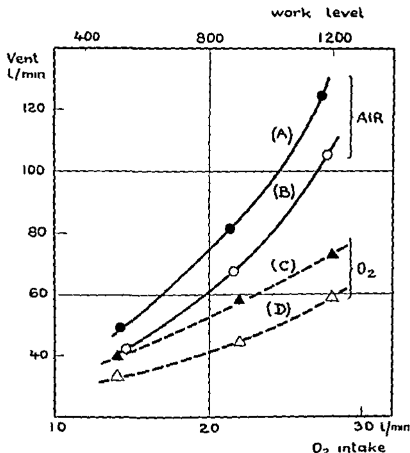


FIG 70 Pulmonary ventilation in relation to oxygen intake at different world levels when breathing air or oxygen at acute exposure (B and D) and on the 4th and 5th days of prolonged exposure (A and C) to 4 000 m simulated altitude A = ventilation when breathing air prolonged exposure B = ventilation when breathing air at acute exposure C = ventilation when breathing 100 per cent oxygen during prolonged exposure D = ventilation when breathing 100 per cent oxygen at 4 000 m before the period of prolonged exposure
Note (1) the marked effect on pulmonary ventilation when oxygen was substituted for air even during the last days of acclimatization (2) the higher pulmonary ventilation attained at a given oxygen intake during the end of prolonged exposure to hypoxia as compared with the values obtained after 10 to 15 minutes of exposure to 4 000 m —(P O Astrand (1954) *Acta physiol scand* 30 343)

heavy work level 66% O was more effective If the effect of oxygen was due to arterial anoxaemia alone then we must infer that the arterial pO was less than 100 mm even when 33% oxygen was breathed This might be explained by an effective venous shunt of 6-11% which as the authors point out seems rather large However as Bannister & Cunningham stated it is possible that cardiac function might be limited by anoxia in heavy exercise (Hill *et al*, 1924) and this might influence the breathing Little is known

about the way in which such relative cardiac insufficiency would produce dyspnœa but it would probably allow the pressures on the right side of the heart to rise and might initiate therefrom reflexes from the right heart or pulmonary vessels (Harrison Harrison & Marsh 1932 Megibow Katz & Feinstein 1943 Mills 1944)

Partially Acclimatized Man in Exercise

Astrand (1954*b*) has reported that the inhalation of pure oxygen by a subject acclimatized for five days at a height of 4 000 metres has a barely significant effect on the pulmonary ventilation volume If however, the subject performs exercise on a bicycle ergometer the substitution of pure oxygen for room air causes an obvious reduction in the pulmonary ventilation for any work level between 600 kg m /min and 1 300 kg m /min as is shown in the accompanying figure (Fig 70) The uncertainty here is whether oxygen is reducing the breathing by reducing a chemoreceptor drive or by reducing cardiac insufficiency which if it is presumed to play a part in exercise at ground level would surely play a much greater one during chronic anoxia This question is surely settled by the fact that a subject suffering from cardiac insufficiency at 600 kg m /min would not be able to perform 1 300 kg m /min at all We may therefore assume that in subjects partly if not completely acclimatized to anoxia the chemoreceptors contribute to the control of the breathing providing the subject is not at complete rest This seems a point of considerable practical importance for people are rarely able to spend much time in complete rest in this busy world

Chapter 19

CARDIOVASCULAR REFLEXES OF CHEMORECEPTOR ORIGIN

Vasomotor Reflexes

Heymans Bouckaert von Euler & Dautrebande (1932) studied the cardiovascular effects of chemoreflex excitation using curarized artificially ventilated dogs The internal and external carotid arteries were tied on one side and the occipital and ascending pharyngeal vessels were also ligated distal to the origin of the arteries supplying the carotid body Great care was observed in avoiding damage of the nerve supply to the glomus On the opposite side the external carotid artery was tied and the carotid sinus nerve was cut (see Fig 65) The intra-carotid injection of 0 5 ml of sodium bicarbonate solution (adjusted to pH = 7 20 by equilibration with CO) caused hypertension when made on the innervated side but was ineffective when made into the carotid artery on the denervated side (Fig 71) Conversely alkaline solutions caused transient hypotension when injected into the innervated side A variety of drugs including lobeline nicotine acetylcholine sodium sulphide sodium cyanide have been shown to cause reflex hypertension when injected in minute doses in the vicinity of the glomus circulation Comroe

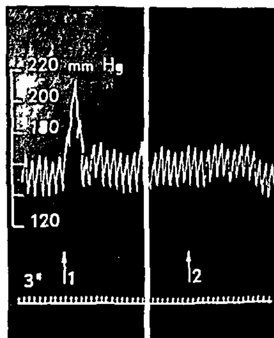


Fig 71 *Dog prepared according to method of Fig 65a* Arterial pressure from femoral artery 1 Injection in normal common carotid artery of 0 5 c c buffered sodium bicarbonate 3 per cent —Hypertension 2 Same injection in carotid sinus denervated common carotid artery No hypertension —(C Heymans J K Bouckaert U S von Euler and L Dautrebande *Arch Intern Pharmacodyn* (193?) 43 186)

(1939) has since identified the site of the aortic chemoreceptors and their blood supply by injecting such drugs into the ascending arch of the aorta Gernandt (1946) recorded action potentials from the aortic nerves of the cat showing the impulse activity aroused by such pharmacological stimulation of the chemoreceptors

Heymans Bouckaert & Dautrebande (1931) found that acute hypoxia (induced by the inhalation of nitrogen) caused systemic hypertension only if the sinoaortic nerves were intact Anoxia caused only vasomotor failure after denervation of the chemoreflex zones Not all workers have confirmed these findings Selladurai & Wright (1932) claimed that the response of the blood pressure of the decerebrate cat to anoxia was rather variable after sino aortic denervation von Euler & Liljestrand (1937) and Dautrebande (1937) found that anoxia might still cause some degree of systemic hypertension in dogs after chemoreceptor denervation Brewer (1937) agreed with Heymans *et al* as did Schmidt (1932) and Comroe (1939)

In general however it may be stated that the stimulant effects of anoxia on the cardiovascular system are exerted mainly via the sinoaortic nerves If the respiration is maintained by artificial ventilation the administration of low oxygen mixtures rarely causes other than depression of the circulation after sino aortic section

Bernthal (1932 1934 1938) has studied the reflex vasomotor effects evoked by chemo receptor stimulation with great care Vasomotor activity was assessed by recording changes of blood flow in the axillary artery by means of a thermo electric method (Bronk & Gesell 1926) Both carotid bifurcation areas were perfused and the vascular isolation was such as to prevent chemical agents introduced into the perfusion circuit from reaching other areas The pressure of blood in the carotid perfusion system and in the axillary perfusion was maintained constant In 71 experiments on 12 animals this perfusion of anoxic blood through the carotid bifurcations caused reflex vasoconstriction of the axillary vessels which became maximal in about thirty seconds Blood equilibrated with 18% O_2 (pO about 130 mm Hg) did not cause reflex vasoconstriction when introduced into the carotid perfusion circuit but blood equilibrated with 15% O or lower con centrations (pO = 110 mm Hg) evoked a reflex response All these responses were obtained in animals whose vagi were cut whose arterial pressure was maintained constant by means of a compensating device and in which ventilation was artificially maintained Histotoxic anoxia produced by the perfusion of cyanide in minute concentrations (0·00055 M) caused abrupt and marked reflex vasoconstriction of the axillary vessels In a later paper Winder Bernthal & Weeks (1938) were the first to show that ischæmia of the carotid body causing stagnant anoxia in the glomus provoked marked reflex vaso constriction of the vessels of the fore limb

Bouckaert Grimson Heymans & Samaan (1941) made a detailed study of the systemic responses of blood pressure and respiration during the inhalation of low O mixtures In dogs lightly anæsthetized with morphine or eucodal in decerebrate dogs or in non anæsthetized dogs systemic anoxic anoxia caused by the inhalation of 8–11 % O_2 in N_2 caused either a slight rise of arterial pressure or did not modify the blood pressure level sensibly Invariably after denervating the chemoreceptor zones anoxia caused a fall of systemic blood pressure The authors noted that after the exclusion of either the aortic or the carotid chemoreceptor zones the systemic blood pressure response to low O_2 mixtures was always pressor They ascribed this phenomenon to the reduction of the

reflex respiratory stimulation which partial chemoreceptor denervation caused Thus when all the chemoreceptors are present, the reflex response of the respiration to low O mixtures may be marked as a result the increased ventilation washes out CO from the blood and the vasomotor centre activity decreases (Dale & Lovatt Evans 1922) Obviously this loss of central activity due to a lowering of pCO must tend to mask the effects of reflex vasoconstriction engendered by anoxic stimulation of the chemoreceptors

Gellhorn Ingraham & Moldavsky (1938) made some striking claims concerning the systemic vasomotor response to anoxia They stated that the rise of systemic blood pressure produced by anoxia varied according to the concentration of blood glucose Hypoglycæmia increased and hyperglycæmia decreased the rise of pressure occasioned by systemic anoxia Van Harreveld & McRavy (1940) claimed that the blood pressure response to anoxia was dependent on the depth of narcosis Lightly anæsthetized animals showed a fall of pressure in those deeply anæsthetized anoxia caused a rise of pressure They concluded that deep narcosis inactivated centres in the higher neuraxis which normally modified the response of the medullary centres to the direct and reflex effects of anoxia They claimed that the results of Gellhorn *et al* (1938) were capable of a similar interpretation indicating that a decreased blood sugar level was merely one cause of supra medullarly depression They may be right but we cannot confirm either their experimental findings or those of Gellhorn Harreveld & McRavy s results are quite different from those of Bouckaert Grimson Heymans & Samaan (1941) Gellhorn s results could not be repeated in some twenty five animals by Özer (unpublished) Striking falls of blood sugar concentration (as low as 20 mg /100 ml) caused by insulin injection had no effect whatever on the response of the blood pressure to anoxia

Bernthal & Schwind (1945) compared the reflex vasoconstrictor responses in the vessels of the leg with those of the intestine during anoxia In animals under artificial constant ventilation the substitution of 10% O in N as the inhalant reduced the flow in the intestinal circuit by 65% If Hering s nerves were blocked the reduction of flow was only 9% The responses were abolished if the four chemoreceptor nerves were blocked Similarly the leg vessels showed vasoconstriction during anoxia providing that the chemo receptors were intact Whereas there were some slight differences in the patterns of the vasoconstrictor responses respectively evoked in the leg and the intestinal circulations it was essentially in the post anoxic phase that differences in behaviour of the two vascular circuits were observed The leg vessels showed a marked and abrupt vasodilatation during which flows reached values 2½ times the pre hypoxic level This post hypoxic vasodilatation was ascribed to a temporary suspension of vasomotor discharge due to the withdrawal of the barrage of afferent chemoreceptor impulses The intestinal vessels on the other hand showed a simple return to the pre hypoxic level Bernthal & Schwind suggested that the absence of post hypoxic vasodilatation in the intestinal circulation was due to local opposition being offered by the mesenteric Pacinian receptors described by Gammon & Bronk (1935) Thus the onset of local vasodilatation would raise the pressure within the intrinsic vessels of these structures and this would reflexly cause vasoconstriction

Bernthal Motley Schwind & Weeks (1945) who studied the vasomotor responses of vessels of the hind limb and the submaxillary gland during carotid glomus perfusion concluded that the thoracolumbar sympathetic outflow represented the sole efferent pathway of the chemoreflex vasomotor reflexes

There have been no studies of the reflex effects of chemoreceptor stimulation on the cardiac output or on venomotor tone It is unlikely that the chemoreflexes cause systemic hypertension only by inducing an increase in arteriolar resistance In this context it is interesting to note the results of Gorlin & Lewis (1954) from their studies of the effects of hypoxia on the cardiovascular system In anæsthetized dogs subjected to various degrees of anoxic anoxia they found that the cardiac output was unchanged providing that the arterial oxygen saturation did not fall below 60% There was an immediate systemic vasoconstriction and hypertension They made no measurements of pulmonary ventilation so it is somewhat difficult to decide on the probable arterial pO_2 However in six dogs the inhalation of 10% O did not lower the arterial oxygen saturation below 60% and the systemic blood pressure rose by 20–35 mm Hg The pulmonary artery and left atrial pressures were measured in these experiments and the pulmonary vascular resistance showed a steady rise During more severe anoxia they noted that the cardiac output increased and providing that the arterial saturation was greater than 40% the cardiac function remained normal during eight hours exposure Systemic hypertension persisted but vasodilatation occurred both in the systemic and pulmonary vessels The increase of pulmonary vascular resistance during anoxia was not very marked in the animals whose arterial saturation exceeded 60% Whether this represents a local effect of anoxia on the vessels or a reflex mechanism induced either from the cardiopulmonary region or from the carotid and aortic bodies remains an open question (see Euler & Liljestrand 1946 Liljestrand 1948 Westcott *et al* 1951 Dirken & Heemstra 1948)

Hæmorrhage

It is doubtful whether the chemoreceptor reflexes exert any significant effects on the circulation at rest It is certain that they contribute to the maintenance of the circulation following a depletion of the blood volume

McDowall (1924) found that the section of both vagi in cats which had been bled severely caused a fall in the systemic blood pressure He noted that Pavlov had made a similar observation in 1879 McDowall attributed this result to the interruption of pressor fibres which arose from receptors in the right atrium These atrial receptors were believed to be stimulated by a fall in the atrial pressure After cocainization of the right atrium he did not observe a fall of blood pressure when he cut the vagi However in the succeeding thirty years no one has found an atrial receptor which is stimulated by a fall of atrial pressure Comroe (1939) suggested that part or all of the McDowall effect was due to the interruption of chemoreceptor impulses from the aortic bodies After denervation of these in one experiment subsequent section of the vagi caused no fall of blood pressure

Coleridge *et al* (1949) and Kenney & Neil (1951) re investigated the problem Cats and dogs were bled until the arterial blood pressure was reduced to 60 mm Hg At this pressure the baroreceptor fibres were considered to be only feebly inactive so their section (together with the other vagal fibres) was not likely to cause a rise of blood pressure Section of the vagi in these bled animals did not always cause a fall of blood pressure which is not surprising when one considers the fibre composition of the vagi Whitteridge (1952) considers that stimulation of the central vagus should be a punishable offence similarly it is foolish to argue closely from the results of cutting the vagi Kenney & Neil chose the best method available—that of cooling the nerves (Partridge 1935 1939) Prior

to this a catheter was introduced via the subclavian artery into the aortic arch or left ventricle and the tip was suitably positioned so that small doses of lobeline injected via the catheter excited the aortic chemoreceptors The beast was then bled to yield a steady mean pressure of 60 mm Hg and the vagi were cooled If the McDowall effect was observed the cooling thermodes were removed and the aortic chemoreceptors were then inactivated by an intraventricular injection of 0 3 ml of 0 5 N acetic acid (Gernandt 1946) Following this inactivation the aortic chemoreceptors no longer responded to the intraventricular injection of lobeline Lastly the vagi were cooled and the response of the blood pressure was noted In none of the experiments was there any fall of blood pressure during vagal cooling after the inactivation of the chemoreceptors although this

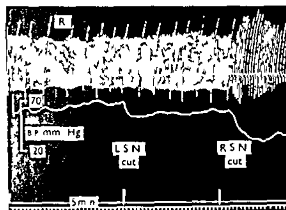


FIG 72 Cat Chloralose anaesthesia Both vagi cut Previously bled 45 ml Records from above downwards respiration blood pressure signal and time in 5 second intervals The effects of successive section of the right and left sinus nerves —(R A Kenney and E Neil (1951) *J Physiol* 112 223)

response had occurred before their inactivation These rather laborious experiments therefore gave results which favoured Comroe s suggestion One would be happier however if there existed more certain knowledge of the detailed distribution of the acetic acid! Nevertheless accompanying evidence presented by Kenney & Neil supports the belief that the chemoreceptors do contribute appreciably to the maintenance of the systemic pressure following hæmorrhage Thus the sinus nerves contain only baroreceptors and chemoreceptors and the baroreceptors are solely active in keeping the blood pressure down In a bled animal with an arterial pressure in the range of 60–80 mm Hg section of the sinus nerves causes a fall of blood pressure (Fig 72) This can only be due to the withdrawal of chemoreceptor reflex vasoconstriction

Landgren & Neil (1951) showed later that hæmorrhage caused strong excitation of the chemoreceptors It seems likely that the chemo vasomotor reflexes play quite an important part following hæmorrhage

It was during these studies that we observed the effect of chemoreceptor denervation on periodic respiration and on the periodic waves occurring in the blood pressure record Rhythmic variations of blood pressure independent of and slower than respiration were first described by Sigmund Mayer (1876) They are confused with Traube Hering waves in the literature Schweitzer was responsible for clearing up this confusion in a short lucid paper in 1945 As he pointed out Traube and Hering separately described periodicity of the blood pressure due to respiration Mayer on the other hand described a much

slower periodicity of the blood pressure particularly likely to be seen in conditions of enfeebled circulation It is these waves which commonly occur in bled animals—they may be accompanied by periodicity of the respiration which occurs at the same rhythm Andersson Kenney & Neil (1950) showed that Mayer waves of enormous amplitude could be evoked by carotid occlusion in animals after previous severe bleeding This had however been previously noted by McDowall (1935*b* 1938) As the systemic blood pressure prior to carotid occlusion was only of the order of 60 mm Hg it was unlikely that clipping the carotids caused any marked change in baroreceptor activity On the other hand chemoreceptor excitation due to glomeric ischæmia was most probable Section of the sinus nerves was therefore carried out upon which carotid occlusion no longer

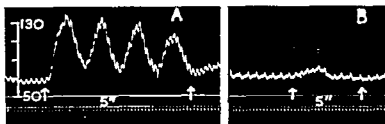


FIG 73 Cat 3 6 kg. Bilateral vagotomy Records from above downwards arterial blood pressure signal line time (5 seconds)
A Effect of occlusion of both common carotid arteries (between arrows)
B Effect of carotid occlusion after selective elimination of the carotid chemoceptors by intra-sinusal injection of acetic acid —(B Anderson R A Kenney and E. Neil (1950) *Acta physiol scand* 20 203)

caused Mayer waves Finally it was shown that carotid occlusion following the selective inactivation of the chemoreceptors by the local injection of acetic acid did not cause Mayer waves (Fig 73) The explanation advanced was as follows ischæmia of the carotid glomera following occlusion caused intense vasoconstriction and a large rise of systemic blood pressure As a result the vicarious circulation of blood through the ascending pharyngeal and external carotid anastomoses (Chungcharoen Daly Neil & Schweitzer 1952 Wang Mazzella & Heymans 1952) improved the carotid body blood flow and lessened the chemoreceptor excitation The blood pressure thereupon fell and carotid body ischæmia once more ensued

Åstrand Green & Neil (unpublished) examined the impulse activity in the chemo receptor fibres together with that in post ganglionic fibres of the superior cervical ganglion Condenser manometer records of the systemic blood pressure and of the blood pressure in the carotid sinus were simultaneously recorded on cathode ray oscillographs In bled animals which showed spontaneous Mayer waves the trough of the wave was attended by a marked increase in chemoreceptor activity and an obvious increase in sympathetic impulse traffic As the blood pressure rose the frequency of the action potentials then diminished

Guyton *et al* (1951) noted that spontaneous blood pressure waves often developed in animals subjected to repeated cycles of withdrawal and re injection of blood They referred to these erroneously as Traube Hering waves and attributed them to reciprocal activity in the baroreceptive and sympathetic nerves As they made no reference to the

paper of Andersson *et al* (1950) they were probably unaware that the circumstances which they induced in their experimental animals were exactly those which would favour the development of Mayer waves of chemoreceptor origin

Reflex Chemoreceptor Effects on the Heart Rate

Heymans Bouckaert & Dautrebande (1931*d*) found that the local injection of cyanide into the carotid body circulation caused bradycardia If the corresponding sinus nerve were cut no change of heart rate took place proving that the slowing of the heart rate was not due to a direct effect of cyanide on the medullary cardiac centres Similar results were obtained with nicotine (Heymans & Bouckaert 1941) although this drug can be shown to have some central stimulant on the cardio inhibitory centre albeit in larger doses than are required to excite the chemoreceptors

Bernthal (1938) Comroe & Schmidt (1938) confirmed these responses to the injection of chemical excitants Comroe & Schmidt (1940) were of the opinion however that the reflex bradycardia thus evoked was the result of stronger chemoreceptor stimulation than that which sufficed for a minimal respiratory response As Bernthal Greene & Revzin (1951) have stated however the literature contains many references to reflex tachycardia produced by chemoreceptor stimulation Thus Asmussen & Chiodi (1941) von Euler & Liljestrand (1942) Whitehorn Edelmann & Hitchcock (1946) Dripps & Comroe (1947) and Alveryd & Brody (1948) are among many who have ascribed a chemoreceptor origin to anoxic tachycardia

Bernthal Greene & Revzin (1951) themselves re investigated the reflex effects on the heart rate of perfusion of the carotid glomus by solutions equilibrated with low oxygen tensions or containing sodium cyanide In their experiments the dogs were either breathing room air spontaneously or were alternately ventilated by room air Slight but definite bradycardia resulted upon anoxic stimulation of the chemoreceptors perfusion of sodium cyanide solutions caused obvious slowing of the heart rate In all cases the slowing of the heart rate was more obvious if concomitant responses of the arterial blood pressure and respiration were prevented by a compensator and by artificial ventilation respectively These results though interesting of themselves throw little if any light on the effects of chemoreceptor stimulation on the heart rate in the circumstances of systemic anoxia As is fully appreciated systemic anoxia providing that it is not of too severe degree causes tachycardia Although Bernthal is quite correct in admonishing those who ascribe this cardiac acceleration in systemic anoxia to chemoreceptor reflexes in the absence of any positive evidence his own experimental results were obtained in animals breathing or ventilated by room air The response of the medullary centres and of the sino atrial node to the effects of chemoreceptor stimulation may be qualitatively different when there is no systemic anoxia (Neil 1951 1954*b* 1956*b* Landgren & Neil 1952) To investigate this point directly Neil (1956) arranged both carotid glomus regions so that they could be supplied alternately by the natural arterial circulation or by perfusion from a reservoir This was effected by introducing T cannulæ into both common carotid arteries All branches given off at the carotid bifurcation were tied except those supplying the carotid bodies The venous drainage of the carotid bodies was carefully preserved The two aortic nerves which contain the majority of the aortic and subclavian chemo receptor fibres (Neil Redwood & Schweitzer 1949*c*) were cut After control observations

of heart rate respiration and blood pressure made while the animals breathed room air systemic anoxia was induced by administering 5% O_2 in nitrogen The characteristic triad of hyperpnœa tachycardia and hypertension was allowed to develop and stabilize whereupon the common carotid arteries were occluded by clips and the carotid bodies were thereupon perfused by oxygenated Ringer Locke solution from the reservoir The mean pressure in the reservoir was identical with that in the systemic circulation immediately prior to perfusion A dramatic reduction of respiration and some fall of blood pressure occurred (Fig 74) The heart rate showed little or no change during the period of perfusion Perfusion was not continued for more than twenty seconds owing to the increase

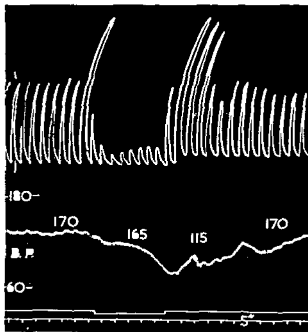


FIG 74 Results of perfusion of both carotid bodies with oxygenated Ringer Locke during spontaneous respiration throughout of 5 O_2 in air
Cat Chloralose anæsthesia vagi intact aortic nerves cut Records from above downwards respiration systemic blood pressure signal and time in 5 second intervals During air breathing prior to the development of anoxic anoxia the control value of mean blood pressure was 125 mm Hg and the control value of the heart rate was 140/min The animal then breathed 5 % O_2 in N for 5 minutes prior to taking this record During the period indicated by the signal the carotid bodies were perfused with oxygenated Ringer Locke solution Note the transient bradycardia which occurs some 10 seconds after the restoration of the circulation of anoxic blood through the carotid bodies (Heart rates are indicated above the systemic blood pressure record) —(E Neil (1956) *Arch int Pharmacodyn* 105 477)

in systemic anoxia due to the hypopnœa which ensued upon the withdrawal of the chemo receptor stimulation On re establishing the systemic arterial blood flow and thereby terminating the perfusion the respiration increased markedly and the systemic blood pressure rose A common feature of this post perfusion period was a transient bradycardia lasting a few seconds which appeared following the initial reflex responses of respiration and blood pressure Unlike the reflex responses of blood pressure and respiration which occurred briskly after the arterial blood gained access to the carotid bodies the change of heart rate appeared some five seconds later It was not closely related to the changes of blood pressure but seemed to be more dependent on the respiratory response usually setting in after the animal had taken two or three deep breaths It was not seen in experiments in which the animals were artificially ventilated throughout It will be remembered that Bronk Ferguson Margaria & Solandt (1936) showed that the impulse traffic in fibres of the inferior cardiac sympathetic nerve was often inhibited by

respiration and the present findings of a relationship between intense respiratory stimulation and bradycardia invites further investigation It is possible that excessive inspiratory movements reflexly evoke bradycardia via vagal stretch receptors of the Hering Breuer type

Nevertheless these experimental results do not support Bernthal s belief that the chemoreceptors are responsible for producing bradycardia in conditions of systemic anoxia Neither do they suggest that the chemoreceptors are in any way involved in the production of tachycardia by systemic anoxia It seems probable that they exert little if any effect on the heart rate in systemic anoxia Additional evidence which indirectly bears on this point is provided from studies of the circulation during carboxyhæmoglobinæmia (Chiodi *et al* 1941) or methæmoglobinæmia (Clark *et al* 1943) In each case tachycardia develops but in neither condition is there any stimulation of the chemoreceptors providing that the respiration or ventilation is adequate to maintain the arterial oxygen tension It seems therefore that the tachycardia of systemic anoxia is due to either *direct stimulation of the sympathetic centres or to effects of the low oxygen tension in the* s a node itself Naturally if the pO falls to very low levels then a direct depressant effect of anoxia on the heart itself causes bradycardia but if the oxygen tension be higher than such a lethal level tachycardia is always seen Sympathetic stimulation of adrenaline secretion by the suprarenal glands in systemic anoxia has not been clearly related to a reflex chemoreceptor origin

Recently Green & Neil (unpublished) have proved that the drugs which cause reflex bradycardia when injected into the carotid bifurcation are all capable of stimulating the baroreceptors of the carotid sinus as well as the chemoreceptors of the glomus This naturally changes the interpretations given by the older authors It is probable that the slowing of the heart is evoked by a baroreceptor reflex

In view of the evidence which already exists that acetylcholine and nicotine can stimulate a variety of nerve endings it is not particularly surprising that the baroreceptors should be activated by these compounds It is rather unexpected on the other hand that sodium sulphide and sodium cyanide should cause such powerful stimulation of these endings

I de Burgh Daly and M de Burgh Daly (1957) have recently reported that the perfusion of venous blood through the carotid bodies causes bradycardia in the dog The animals were ventilated artificially and the chest was opened in the mid sternal line In view of these results which support those of Bernthal it seems that marked stimulation of the glomus receptors causes bradycardia in the dog artificially ventilated with room air Whether a species difference in the reflex cardiac response to chemoreceptor stimulation exists between the cat and the dog (as suggested by Neil 1956) requires further investigation Similarly more evidence of the effects of severe anoxic stimulation of the chemoreceptors on the heart rate of dogs exposed to systemic anoxia would be desirable

CHAPTER 20

THE MODE OF STIMULATION OF THE CHEMORECEPTORS

The chemoreceptors are stimulated by anoxia hypercapnia and by acidosis

Anoxia

As has been stated the chemoreceptors are stimulated by anoxic stagnant and histotoxic anoxia but not by anæmic anoxia Comroe & Schmidt (1938) who were the first to show that anæmic anoxia was ineffective in exciting chemoreflex responses concluded from their results that the small amount of oxygen dissolved in the plasma was sufficient to satisfy the needs of the glomus cells providing that the tension of the oxygen was normal This conclusion which was natural enough suggested however that the metabolic needs of the glomus cells were very modest for the amount of oxygen dissolved in the plasma is only of the order of 0 3 ml /100 ml The direct measurement of bloodflow and oxygen usage of the carotid body by Daly Lambertsen & Schweitzer (1954) has led to a revision of this opinion The carotid body is the most vascular tissue in the organism with a bloodflow of 2 000 ml /100 g /min and its oxygen usage is 9 ml /100 g /min These figures seem very high but if the blood flow occurs partly through shunts as de Castro described then the oxygen usage would be higher still As Daly and his co workers point out the huge blood flow allows the carotid body to maintain a high oxygen consumption although extracting very little oxygen from each 100 ml of blood They argue that in terms of oxygen flow to the body it is immaterial whether the blood flow be reduced or whether the content of O /100 ml blood be lessened providing that the oxygen tension be maintained in each case Making a comparison of these two types of reduction they point out that Duke *et al* (1953) found little if any chemoreceptor discharge in carboxyhæmoglobinæmia when 75% of the hæmoglobin was combined with carbon monoxide—the oxygen flow being therefore only a quarter of the normal Landgren & Neil (1951) however found that hæmorrhage which lowered the systemic pressure from 130 to 90 mm (which from the results of Daly *et al* would lower blood flow and therefore oxygen flow to a quarter) caused intense firing of the chemoreceptors which was soon dispelled by raising the oxygen tension The discrepancy here which Daly *et al* could not explain may be due to the accumulation of CO and/or other metabolites in the conditions of stagnant anoxia (hæmorrhage) which does not occur in the conditions of anæmic anoxia Having once shown that the carotid body has a high rate of metabolism we must perforce believe that the production of CO and/or other metabolites is correspondingly fast and this will lead to a rapid accumulation as their rate of removal by the blood flow is lessened As the inhalation of pure oxygen considerably lessens the chemoreceptor discharge after hæmorrhage this suggests that the metabolites causing the discharge are anærobic it does not support the belief that CO is the responsible agent A further point of argument is found in the well known experimental finding (Bogue & Stella 1935) of the persistence

of intense chemoreceptor discharge for as long as thirty minutes after death In such circumstances the high rate of metabolism of the carotid body must exhaust its own tenuous reserves of foodstuffs very quickly—it is the rapid accumulation of metabolites which cannot then escape which maintains the excitation of the chemoreceptor nerve endings

A very rare finding obtained once by the present author and once by Landgren (personal communication) may be cited here to illustrate how stagnant anoxia due to a low systemic pressure may cause heavy chemoreceptor discharge in animals ventilated by 100% O_2 The accompanying figure (Fig 75 (Landgren)) shows chemoreceptor activity

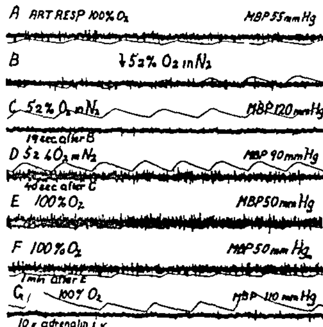


Fig 75 Cat Chloralose urethane anaesthesia Right carotid sinus nerve cut centrally and chemoreceptor fibre slip used for recording Blood pressure recorded from external carotid artery by condenser manometer A B C D E F G are segments of film recorded during the artificial ventilation of various gas mixtures Note that 5 per cent O_2 ventilation reduces the chemoreceptor discharge (and raises the systemic pressure) 100 per cent O_2 lowers the systemic pressure and increases the chemoreceptor discharge In G 10 µg Adrenaline has been given and raises the blood pressure—no baroreceptor discharge occurs —(S Landgren)

in a cat ventilated by 100% O_2—the systemic B P is only 50 mm Hg and there is a heavy discharge of impulses *On substituting 5% O_2 in N_2 as the ventilation gas mixture the* systemic pressure rises to 150 mm Hg and the chemoreceptor discharge becomes much less despite the low pO_2 Restoration of 100% O_2 is followed by a fall of blood pressure and a return of the impulse activity Presumably the reduction in local blood flow *produced by the lowering of the systemic blood pressure caused a local accumulation of* metabolites which outweighed the effects of the rise of oxygen tension Similar results were obtained after cutting the homolateral cervical sympathetic trunk

Carbon Dioxide

Samaan & Stella (1935) von Euler Liljestrand & Zotterman (1939) and Bartels & Witzleb (1956) have shown that the chemoreceptor impulse activity increases linearly with increases of carbon dioxide pressure above about 30 mm Hg The discharge in response to raised CO_2 tension is rarely as great as that initiated by anoxia Many have suggested that the common stimulus to the chemoreceptors is a rise in the intracellular hydrogen ion concentration in the glomus cells Thus von Euler *et al* showed that the

chemoreceptor discharge aroused by either anoxia or by hypercapnia could be quickly dispelled by the intravenous injection of ammonium hydroxide Winterstein (1955 1956) is the strongest exponent of the intracellular pH hypothesis

Winder (1937) has claimed that the chemoreceptor response to anoxia can be artificially separated from that to hypercapnia by the perfusion of sodium iodoacetate through the glomus Following such treatment local glomus anoxia no longer induced reflex hyperpnœa although hypercapnia in the glomus circulation was still effective in arousing reflex responses of the breathing Winder suggested that anoxic stimulation of the glomus nerve endings was normally achieved by the accumulation of some acid metabolite formed by anærobic glycolysis Monoiodoacetate was presumed to block the glycolytic chain and hence the acid metabolite was no longer produced Carbon dioxide continued to act as an effective stimulant by virtue of its direct effect on the intracellular pH Åstrand Green & Neil (unpublished) were unable to dissociate the chemoreceptor responses to anoxia and hypercapnia by using monoiodoacetate Invariably the loss of response to anoxia was accompanied by a disappearance of that to hypercapnia The first appearance of monoiodoacetate in the glomus circulation itself induced an outburst of chemoreceptor potentials This was not due to the pH of the perfusing solution Landgren Liljestrand and Zotterman (1954) also noted that the intra carotid injection of 2 mg sodium iodoacetate caused heavy though temporary discharge whereas a dose of 10 mg paralysed the nerve endings Anitchkov (1953) also reported that iodoacetate abolished the chemoreceptor response to oxygen lack

Neil (unpublished) recently obtained a pure chemoreceptor preparation containing very few fibres in which there was a response of one unit to anoxia but not to hypercapnia another unit discharged actively during hypercapnia but showed no unequivocal response to anoxia (Fig 76) It seems unlikely that there should be two types of glomus receptors one responding to hypercapnia and the other to anoxia On the other hand de Kock has described two types of glomus cell and has stated that Type I is much the more common It is possible that the stronger chemoreceptor discharge seen in multifibre recordings during anoxia compared with that to hypercapnia may be due to a preponderance of units which are affected by anoxia only However de Kock has stated that the Type I and Type II glomus cells are often innervated by the axon terminals of one and the same Cajal interstitial cell and this hardly favours such a hypothesis as is mentioned above More studies of single chemoreceptor units responding to anoxia and/or hypercapnia are required

Bernthal & Weeks (1938) perfused the carotid body with blood at different temperatures and showed that blood equilibrated at 38°C caused reflex hypernoea whereas the same blood perfused at 18°C did not They inferred that this difference could be attributed to the effect of temperature on the metabolic rate of the glomus cells Schmidt & Comroe (1940) seriously criticized their conclusions pointing out that blood cooled anærobically showed a large change of pH to the alkaline side (Martin & Lepper 1926 Stadie & Martin 1924 Warburg 1922 Adair Cordero & Shen 1929 Brewin Gould Nashat & Neil 1955) Blood cooled anærobically from 38°C to 18°C would increase its plasma pH by 0 294 (Rosenthal 1948) Hence as Schmidt & Comroe said the results of Bernthal & Weeks may well have been due to this change in pH Nashat & Neil (1955) showed that the chemoreceptors still responded feebly to anoxia or to sodium cyanide

when the whole animal was cooled to a temperature of 26°C Between 26°C and 20°C body temperature the chemoreceptors ceased to respond

Shen & Hauss (1939) used the drug 2 4 dinitrophenol as a metabolic stimulant in order to excite the chemoreceptors 0 4 mg in 0 2% solution caused intense reflex hyperpnœa when injected into the common carotid artery providing that the corresponding sinus nerve was intact The effects noted could not be ascribed to the acidity of the solution for 0 8 mg of trinitrophenol which is more acid was ineffective on intracarotid injection Jarisch Landgren Neil & Zotterman (1952) confirmed these findings Shen &

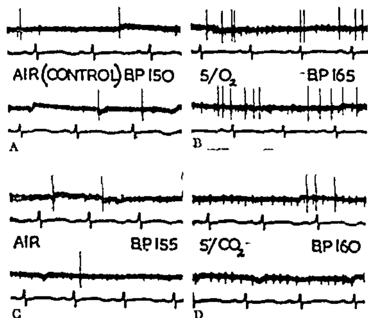


FIG 76 A B C D each show two segments of film recorded during spontaneous breathing of gas mixtures stated Each film strip shows electro neurogram above and E C G below
Note that large potential increases its impulse discharge during anoxia but is virtually unaffected by CO excess The small potential is little affected by anoxia but discharges steadily during hypercarbia —(E Neil)

Hauss ascribed their results to the stimulant effect of dinitrophenol on the metabolic activity of the glomus cells Anitchkov and his co workers have extended these studies and while confirming the results interpret them somewhat differently The drug acts by inhibiting the re synthesis of energy rich phosphate compounds (see Section on Drugs) There is no doubt that chemoreceptor activity can be aroused by an increase in the hydro gen ion concentration of the blood as was first shown by Heymans Bouckaert & Dautre bande (1931) Conversely chemoreceptor activity induced by anoxia or hypercapnia can be dispelled by the intravenous injection of ammonia However it is not proven that the chemoreceptor endings are excited by changes of the pH in the glomus cells themselves Changes of acidity of the blood may act by modifying glomus cell metabolism so that an accumulation of intermediate metabolites occurs

Schmidt (1941) attempted to account for the site and for the chemical sensitivity of the chemoreceptor areas by postulating that they were originally developed in aquatic forms He considered that they were situated in the branchial arches Marshall & Rosenfeld (1936) had made a less precise reference to the evolutionary origin of the chemoreceptors Noting that respiration in deeply anæsthetized mammals was maintained

by anoxic stimulation of the chemoreflex zones they suggested that in these abnormal conditions the respiration was taken over by more primitive reflex mechanisms which were themselves probably of more fundamental importance in remote ancestral forms They quoted Babak (1909) who found that the respiratory movements of the tadpole were extremely responsive to changes of oxygen tension in the environment but were little affected by alterations in the carbon dioxide tension Schmidt argued that a branchial chemoreceptor system would have an obvious advantage in sampling the chemical composition of the environment Furthermore if some such system did exist it would be to the organism s advantage to have it regulated by changes in the tissue tension of oxygen rather than carbon dioxide for the latter is so very soluble in water at ordinary temperatures that an increase in the tension of the gas would be unlikely to occur in water as the result of stagnation or pollution until the oxygen tension had been dangerously reduced He considered that the importance of the chemoreceptor zones in the mammal lay rather in their ability to withstand and respond to adverse circumstances which would damage the central neurones than in their possessing exquisite sensitivity to the factors which normally regulate breathing Schmidt s conception of the developmental origin of the chemoreceptor zones is similar to that of Koch (1931) in the case of the baroreceptor areas There is a great deal of positive evidence for Koch s hypothesis but there is as yet none for that of Schmidt Boyd (1936) denies that there is any paraganglionic or chemoreceptor tissue in the branchial arches of the elasmobranch *Mustelus* and claims that such tissue first makes its appearance in the amniotes (birds reptiles and mammals) Nevertheless Schmidt s hypothesis is attractive and deserves testing in physiological experiments on piscine and amphibian forms

Krogh (1941) states that there is no doubt that oxygen lack stimulates respiration in fish (Westerlund 1906 Heerdt & Krijgsman 1939) The effect of CO on the other hand is doubtful and is never very pronounced (Olthoff 1934 Meyer 1935) Van Dam (1938) made a very complete study of the chemical control of respiration in the eel *Anguilla vulgaris* and the trout *Salmo shasta* The ventilation increased up to five fold when the oxygen content of the water fell below 4 ml /l Two of his three eels showed an increase in ventilation volume when 5 / CO_2 was bubbled through the water in the remaining eel CO caused inhibition The trout increased their ventilation only slightly when 1–1½% CO was bubbled through the water and no tests could be made at higher concentrations as the solution became irritant Van Dam considered that CO dyspnœa would be unlikely to occur in clean natural water as the CO tension therein is at most 1–2 mm Hg (Krogh & Leitch 1919)

One of the most fascinating forms of adaptation in respiratory control of fish is found in the yarrow *Erythrinus* which inhabits tropical swamps The yarrow is exposed to a very low oxygen tension and a very high CO_2 tension in its aquatic environment and has developed an accessory breathing organ for aerial respiration Willmer (1934) made a classical study of the relations between the gas content of the water and the mode of respiration—aerial or branchial At low CO tensions aerial respiration superseded branchial even when the oxygen content was high Apparently in this creature the CO tension had to lie between 10–25 mm Hg to stimulate branchial movement at all Krogh (1941) regarded this as a unique adaptation among fish and considered that it foreshadowed the regulatory mechanisms seen in higher forms

Acetylcholine and the Transmission of Chemoreceptor Impulses

Schweitzer & Wright (1938) posed the question whether drugs or changes in the blood which stimulate these (chemoreceptor) nerve endings produce their effects by liberation of acetylcholine as the chemical intermediary This suggestion has received the support of the Swedish workers von Euler Liljestrand & Zotterman 1939 1941 Zotterman 1944 Landgren Liljestrand & Zotterman 1952 1954 Heymans Bouckaert & Pannier 1944 refuted it Euler Liljestrand & Zotterman (1941) found that 5–10 μg acetylcholine introduced into the external carotid artery induced a massive volley of short duration of chemical impulses without influencing the great pressure spikes as they referred to them This is often but not always the case Diamond (1955) has since shown that ACh is perfectly capable of stimulating baroreceptors Zotterman (1944) showed that the effect of ACh in causing chemoreceptor discharge was specific as he found that the intra arterial injection of acetylcholine did not stimulate the afferent nerve endings in the tongue Against this is the evidence advanced by Brown & Gray (1948) that acetylcholine can stimulate nerve endings in the skin and Diamond s evidence that ACh can stimulate the baroreceptors Liljestrand (1951) found that the local application of 0 1–0 2% eserine salicylate to the carotid bodies soon led to an increased respiratory response to oxygen lack and carbon dioxide excess whereas local application of 1% atropine sulphate abolished the response to these stimuli Euler Liljestrand & Zotterman (1939, 1941) suggested that the drugs ACh lobeline and nicotine acted in a manner similar to that in which they affected the sympathetic ganglia Liljestrand (1951) pointed out that the glomus cell and the intra cellular nerve ending formed a synapse Landgren *et al* (1952) found that the chemoreceptor impulse activity produced by anoxia was greatly intensified by the close arterial injection of anticholinesterase drugs This effect was obtained regularly when eserine prostigmine DFP TEPP ergotamine, morphine and sodium fluoride were injected Conversely the injection of atropine curarine tetraethylammonium and decamethonium decreased or abolished the effect of anoxia on the chemoreceptor impulse activity They considered that these results supported their view that acetylcholine played a role as the chemoreceptor transmitter of impulses in the carotid body and that the nervous endplates corresponded to functional synapses They claimed once more that the large baroreceptor spikes were not influenced by autonomic drugs in the concentrations used This is only a question of the difficulty of access however (see Diamond 1955) Douglas (1952) claimed that the intravenous injection of hexamethonium abolished the reflex response of hyperpnœa normally evoked by the local injection of ACh into the glomeric region although the reflex response to oxygen lack was unaffected Heymans Delaunois *et al* (1953) denied this Douglas (1954 suggested that the chemoreceptor nerve endings like other nerve endings could be stimulated by ACh but considered that this non specific sensitivity had nothing to do with their normal mode of stimulation Douglas & Gray (1953) showed that hexamethonium abolished the sensitivity of the carotid chemoreceptors and the tactile receptors in the skin to ACh but had no effect on the response of these nerve endings to their normal physiological stimuli

It would seem that there is much to be said against the hypothesis that ACh is a transmitter of the chemoreceptor Daly (1954) has suggested that the effects of anti cholinesterases in inducing or in potentiating responses of the chemoreceptors may be due to their effect in increasing the synaptic transmission of sympathetic impulses relaying

in the superior cervical ganglion and destined to cause vasoconstriction of the afferent vessels of the carotid body This effect is not important however for the chemoreceptor discharge in response to physostigmine is still seen after the removal of the superior cervical ganglion and its efferent branches (Neil unpublished)

According to Hollinshead & Sawyer (1945) the carotid body contains non specific as well as specific cholinesterase there being a preponderance of the former They found that the true or specific cholinesterase activity was far lower than that for the superior cervical ganglion Koelle (1950) reached the same conclusion using histochemical methods and pointed out that the presence not only of the specific but also of the non specific cholinesterase indicated some important function It is not clear what he means

Meanwhile large quantities of ganglionic blocking drugs continue to be used in attempts to influence the sensitivity of the chemoreceptors Moe *et al* (1948) found that TEA prevented chemoreceptor responses to ACh and nicotine but not to cyanide or anoxia Boelaert (1948) could not confirm this and neither could Heymans *et al* (1953) Indeed Heymans and his co workers could not find that large doses of TEA hexamethonium methantheline or pendiomid had any significant effect on the reflex chemoreceptor respiratory effects of ACh or cyanide It is the authors opinion that ACh has nothing whatever to do with the normal transmission of the chemoreceptor impulses The reasons for the conflict of evidence concerning the effects of anticholinesterases and ganglioplegic drugs on the activity and sensitivity of the glomus nerve endings to normal or pharmacological stimuli require further clarification

CHAPTER 21

THE EFFECTS OF DRUGS ON THE CHEMORECEPTORS

IT is difficult to classify the drugs which have been shown to excite the chemo receptors because of the great variety of chemical structures they possess The following classification though inadequate provides a basis for discussion

1 Alkaloids

(a) Nicotine Heymans & Heymans (1927) showed that nicotine stimulated peripheral receptors located in the aortic arch area and caused reflex excitation of the respiratory centre Heymans Bouckaert & Dautrebande (1931b) extended these findings in showing that nicotine excited the carotid glomus receptors (Fig 77) These findings have been widely confirmed Heymans & Bouckaert (1941) showed that both α nicotine and β nicotine are effective

(b) Lobeline acts similarly to nicotine (Heymans Bouckaert & Dautrebande 1931) Iso lobinine (Pannier & Backer 1945) is a very effective stimulant

(c) Piperidine (Gernandt 1946) excites both aortic and carotid chemoreceptors

None of these drug actions is prevented by atropine Mercier Rizzo & Delphaut (1934) Anitchkov (1937) Comroe & Schmidt (1938) and Philippot (1937) all noted the coincidence between drugs with nicotinic properties and drugs with an ability to excite the chemoreceptors Euler Liljestrand & Zotterman (1939) found that the discharge aroused in chemoreceptor fibres by lobeline or nicotine was not diminished by the intravenous injection of ammonia while that caused by the physiological stimulation of O lack or CO_2 excess was abolished this led them to the belief that the alkaloids stimulated hypothetical ganglion cells interposed on the chemo receptor fibre pathway

(d) Curare abolishes the effect of nicotine on the chemoreceptors (Anitchkov 1947)

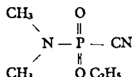
(e) Anabasine coniine and cytisine are among other alkaloids which stimulate the chemo receptors (Anitchkov 1935 1937)

2 "Metabolic Drugs"

(a) Cyanides

Heymans Bouckaert & Dautrebande (1931b) and Euler & Liljestrand (1937a) found that cyanide is a strong chemoreceptor stimulant This drug is generally used for testing the chemoreceptor reflexes and is given in minute doses by close intra arterial injection The chemoreceptor discharge caused by cyanide is abolished or reduced by the intravenous injection of ammonia (Euler Liljestrand & Zotterman 1939) and is reduced by the inhalation of 100% O

Tabun (dimethylamido ethoxy cyano phosphine oxide)



a substance developed for military purposes causes a fleeting hyperpnœa when introduced into the circulation of the carotid body Its chemical excitant effect is due to the cyanide content of the molecule (Heymans Pochet & Van Houtte 1956)



FIG 77 Monkey anæsthetized with morphine-chloralose Right carotid sinus nerve cut R = respiration P A = arterial pressure 1 = injection in left normal innervated common carotid artery of 0 1 mg nicotine Marked hyperpnœa and rise of arterial pressure 2 = same injection in right denervated common carotid artery No hyperpnœa and no rise of arterial pressure —(A Verdonk (1937) *C R Soc Biol* 126 431)

According to Anitchkov (1947 1951 1955) sodium cyanide acts on the cytochrome cytochrome oxidase system Anitchkov suggested on this basis that the hæmin ferment system of the type of cytochrome cytochrome oxidase plays the role of chemoreceptor in the carotid body Curare which completely blocks the action of acetylcholine and nicotine on the carotid bodies (Anitchkov 1947) has little if any effect on the cyanide response of the chemoreceptors Eserine does not increase the action of potassium cyanide on the carotid bodies as it would be expected to do if ACh were a mediator Atropine has no effect on the response of the chemoreceptors to cyanide and neither does hexamethonium (Anitchkov 1951) If cyanide solutions

are perfused through the carotid body for long they paralyse the chemoreceptors (Melnikova 1947) According to Anitchkov (1955) sulphides act similarly to cyanides (see also Iwase & Yamanouchi (1951))

(*b*) **Drugs with reducing properties**

Hydroxylamine paramino phenol hydroquinone and reduced codehydrase have all been shown by Belenky (1949*a*) to stimulate the chemoreceptors Belenky relates this to their reducing properties

(*c*) **" Dissociative " poisons**

Such substances are referred to by Anitchkov and his school as having the property of impairing the coupling of tissue respiration and phosphorylation In spite of the continuation of oxgyen consumption the generation of new macroergic phosphate connections is inhibited Four such drugs were shown to be effective stimulants of the carotid body by Seitz & Engelhardt (1949) 2 4 dinitrophenol sodium azide sodium nitrite and methylene blue 2 4 dinitrophenol (Shen & Hauss 1939) and sodium nitrite had been previously shown to be chemoreceptor stimulants by Heymans & Bouckaert & Dautrebande (1931) Sodium azide and methylene blue were also described as exciting the glomus cells by Anitchkov (1945) and Belenky (1949*b*) On the grounds of their common property of causing chemoreceptor stimulation Anitchkov (1951) considered it possible that chemoreceptor excitation occurred when there was a disturbance between the equilibrium between the resynthesis of macroergic phosphate compounds and their rate of breakdown The chemoreceptor stimulation by anoxia might he thought be similarly explained macroergic phosphates were disrupted but no resynthesis occurred

(*d*) **Adenosine triphosphate**

ATP was shown to excite the chemoreceptors by Jarisch Landgren Neil & Zotterman in 1952 Anitchkov (1951) quotes Belenky (1951) as showing that a preliminary perfusion of ATP in concentrations of 10^{-6}–10^{-8}M through the *isolated carotid bifurcation greatly increased the chemoreceptor response to the sub*sequent exhibition of cyanide lactic acid or ACh Belenky also showed that the excitability of carotid body chemoreceptors exhausted as a result of long perfusion with cyanide could be restored by means of ATP perfusion The intensity of the reflex responses from the carotid body in response to the various stimuli was thus related to the ATP content of the glomus cells as this fell to zero the chemoreceptor cells became inexcitable

(*e*) **Glycolytic poisons**

Winder (1937) first showed that monoiodo acetate abolished the response of the chemoreceptors to anoxia He claimed that selective concentrations of this enzyme inhibitor would abolish the response to anoxia without suppressing that to CO excess This interesting finding was used by Gesell (1939) to bolster the hypothesis that the chemoreceptor activity was controlled by the intracellular acidity

Anoxæmia and cyanidæmia which are known to cause an accumulation *of lactic* acid when anaerobic glycolysis is prevented by localized poisoning with mono iodo acetic acid increased breathing is missing (from anoxia) though hyperpnœa is still produced by localized hypercapnia These results and their interpretations were

criticized by Schmidt & Comroe (1940) Åstrand Green & Neil (unpublished) could never succeed in abolishing the chemoreceptor response to oxygen lack without simultaneously losing that to CO excess Anitchkov (1953) confirmed the loss of response to anoxia following monoiodoacetate and noted that monobromacetate was equally effective Jarisch *et al* (1952) noted that the intra carotid injection of 2 mg sodium iodoacetate in cats was followed by an enormous increase of chemo

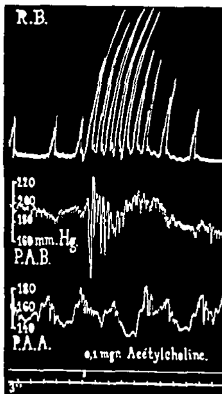


FIG 78 Isolated but innervated carotid sinus and body area of dog B perfused by means of dog A (Fig 15) R = respiration of dog B P A B = arterial pressure and heart rate of dog B P A A = arterial pressure of dog A I = injection of 0 1 mg acetylcholine in circulation of perfused carotid sinus of dog B—Marked reflex hyperpnœa and bradycardia in dog B —(C Heymans J J Bouckaert S Farber and F Y Hsu (1936) *Arch int Pharmacodyn* 54 129)

receptor impulse activity whereas the injection of larger amounts (10 mg) abolished chemoreceptor discharge for some minutes Anitchkov (1953) includes sodium fluoride sodium arsenite and sodium malonate with iodoacetate as glycolytic poisons which abolish or reduce chemoreceptor excitability After prolonged perfusion with such solutions chemoreceptor activity can be restored by adding ATP to the perfusing fluid From these results Anitchkov has stressed his claim that the glomus cells are dependent on a normal carbohydrate metabolism Disturbance of the balance between dissimilation of macroergic phosphates and their resynthesis or disturbances in the cytochrome cytochrome oxidase system causes chemoreceptor activity—providing that carbohydrate stores or supplies are adequate and that the breakdown of sugar intermediates is not prevented

This hypothesis of the Russian School whilst it leaves many lacunæ in our understanding of the mechanism as a whole seems to us to be much more profitable

than that based on the responsiveness of the chemoreceptor nerve endings to acetylcholine As is argued elsewhere it would seem that any nerve ending is stimulated by ACh and the chemoreceptor nerve endings prove no exception

3 Acetylcholine, choline derivatives and related compounds

Dautrebande & Marechal (1933) found that carbaminoyl choline strongly excited the carotid chemoreceptors and their findings were widely confirmed Anitchkov and his co workers (1936) and Heymans Bouckaert Farber & Hsu (1936) obtained similar results with acetylcholine (Fig 78) and all subsequent workers have agreed with their claims Philippot (1937) found that a large variety of drugs of the choline series with nicotinic properties were chemoreceptor excitants Schweitzer & Wright (1938) showed that atropine did not abolish the response to ACh and Winder confirmed this (1938) Philippot & Dallemagne (1950) found that the monophenolic ether of homo iso muscarine was a stimulant De Wispelaere (1937) showed that acetyl β methylcholine ethyl β methylcholine and ethylcholine were chemoreceptor excitants

Liljestrand (1951*a* *b*) showed that the local application of a 1% solution of atropine sulphate on the carotid bodies caused a great decrease in the chemoreceptor response to anoxia or to lobeline and ACh The intravenous injection of large doses of atropine on the other hand did not modify these chemoreceptor responses This latter finding confirmed earlier work of Schweitzer & Wright (1938) and Euler Liljestrand & Zotterman (1941) Heymans Delaunois Martini & Janssen (1953) however showed that the topical application of such strong concentrations of atropine to the carotid bifurcation caused a local anæsthetic action with the result that the systemic blood pressure rose (due to abolition of baroreceptor discharge) and the animal failed to show any reflex chemoreceptor respiratory responses

4 Anticholinesterases

Eserine injected in the vicinity of the carotid body enhances the sensitivity of the chemoreceptors to ACh but not to lobeline (Heymans Bouckaert & Pannier 1944) or to cyanide (Asratian 1938) Verbeke (1949*a* *b*) obtained similar results with DFP and TEPP which sensitized the glomus cells to ACh but not to cyanide (1949) Verbeke & Votava (1949) found that HETP TEPP and Nu 683 increased the chemoreceptor sensitivity to ACh Atanackovic (1950 1951) showed that the tetra methoquinine methiodide sensitized the chemoreceptors to ACh but not to lobeline sulphide or cyanide Casier & de Vleeschhouwer (1952) stated that the chlorphenylmethyl carbamate of hydroxyphenyltrimethylammonium inhibits pseudocholinesterase completely and selectively having no influence on true cholinesterase This drug sensitizes the chemoreceptors to ACh The dimethyl carbamate of hydroxyphenyltrimethylammonium is also a potent anticholinesterase and sensitizes the carotid body to ACh but not to sodium sulphide (Atanackovic & Dahlgaard-Mikkelsen (1950) Caldeyro & Garcia Austt (1952) Mazzella & Migliaro (1949) and Fernandez (1949)

5 Ganglioplegic drugs

Tetraethylammonium was claimed to inhibit the chemoreceptor stimulation induced by ACh nicotine and lobeline but not that evoked by anoxia (Moe Capo & Peralta 1948) Boelaert (1948) could not confirm this

Douglas (1952) claimed that hexamethonium given intravenously in high doses abolished the response of the chemoreceptors to ACh lobeline and nicotine and did not affect their response to cyanide or anoxia Landgren Liljestrand & Zotterman (1952) found that very high doses of tetraethylammonium or decamethonium injected locally into the carotid body abolished or reduced the chemoreceptor response to lobeline ACh and anoxia but pointed out that the effect was more pronounced in the case of ACh or lobeline

Heymans Delaunois Martini & Janssen (1953) found that large doses of tetra ethylammonium metaneline or pendiomide did not affect the respiratory responses to chemoreceptor stimulation by ACh lobeline or cyanide

Dontas & Nickerson (1954) on the other hand found that small doses of ganglio plegic drugs (tetraethylammonium pentamethonium hexamethonium pendiomide and Arfonad) effectively blocked the chemoreceptor response to ACh and lobeline, and prolonged the response to hypoxia and cyanide

Deca hexa and pentamethonium effects on the chemoreceptor action potentials in cats were reported by Gollwitzer Meier & Witzleb (1953) Pentamethonium inhibited the response to anoxia lobeline or ACh Decamethonium had no action in reasonable doses Budde (1954) injected moderate or large amounts (1–20 mg) of tetraethyl ammonium into the carotid artery in cats and recorded chemoreceptor action potentials The impulse activity aroused by anoxia was unaffected that evoked by ACh was abolished

We are somewhat dubious about the effects of huge amounts of these drugs given locally into the carotid circulation We feel that the pH of the solutions used and the bromide or iodide ion of the compounds may be complicating the responses seen in these conditions

6 Miscellaneous drugs

5-Hydroxytryptamine (serotonin) stimulates the chemoreceptors according to Douglas & Toh (1952) Heymans & Van den Heuvel Heymans (1953) could not confirm this McCubbin Green Salmoiraghi & Page (1956) however found that 12 micrograms given into the common carotid artery induced carotid chemoreceptor discharge The drug was described as a more powerful stimulant than lobeline tryptamine or DMPP *Its action like that of anoxia was not blocked by TEAC* There seems some variation in the chemical properties of various preparations of 5 hydroxytryptamine Each of us has separately tried the effect of injecting this substance into the glomus circulation with negative results Green participated in the experiments at the Middlesex Hospital these showed that a chemoreceptor preparation which responded briskly to the usual stimulant (cyanide and lobeline) gave no response to serotonin Green however later obtained most striking responses in collaboration with McCubbin Salmoiraghi & Page

Veratrum alkaloids have been shown to excite the chemoreceptors by Jarisch & Richter (1939) Krayer & Acheson (1946) Aviado Pontius & Schmidt (1949) Heymans & de Vleeschhouwer (1950) Cerletti Li Alanis & Aviado (1951) Jarisch Landgren Neil & Zotterman (1952) Witzleb (1952) Rothlin & Cerletti (1954) and Martini & Callhauw (1955)

Phenyl diguanide was shown to stimulate the chemoreceptors by Dawes Mott & Widdicombe (1952) Heymans Hyde Terp & De Vleeschhouwer (1952) did not confirm this observation

Histamine According to Fabinyi & Szebehelyi (1948) anoxic hyperpnœa can be prevented by cholesterol by Antistine or by desensitization to histamine These observations suggested that histamine might be concerned with the stimulation of the chemoreceptors by anoxia Å Liljestrand (1949) did not confirm this The intra venous injection of lergitine in doses that abolished the action of intravenous injections of histamine on the systemic blood pressure had no effect on the systemic blood pressure and no effect on the respiratory response to hyperpnœa Landgren Liljes trand & Zotterman (1954) moreover could demonstrate no influence of histamine (administered by carotid injection) on the chemoreceptor impulse discharge and could find no effect of antihistaminic drugs on the chemoreceptor or potentials evoked by anoxia

Zunz & Tremonti (1931) showed that the stimulation of the respiration produced by Coramine (nikethamide) was due partly to an action on receptors in the carotid bifurcation (i e chemoreceptors) and partly to a central action on the medullary neurones Pentamethylenetetrazol (Cardiazol) on the other hand caused respiratory stimulation which was unaffected by the presence of the sinus nerves and therefore acted directly on the respiratory centre

Abdominal Chemoreceptors

Latschenberger & Deahna (1876) were the first to suggest that respiratory reflexes might be initiated by chemical stimulation of nerve endings situated in the peripheral vasculature Others later claimed that circulatory responses could be similarly produced in addition to those of respiration (Spalitta and Consiglio (1892) Heger (1887) Pagano (1900) Siciliano (1900)) In general such claims are based on the demonstration of circulatory or respiratory responses to the intra arterial injection of large amounts of strongly irritant chemicals There is no proof that the reflex effects were due to the stimu lation of nerve endings in the vascular walls It is quite possible that pain or other nerve endings in the perivascular tissues were stimulated in these conditions

Recently Tchernigovsky (1954) revived the idea that chemical excitation of receptors in the peripheral vascular system evoked respiratory and circulatory reactions Acetyl choline nicotine procaine and sodium cyanide were effective in this respect when introduced into the isolated circulation of the limbs spleen intestine kidney, adrenal testis thyroid or pancreas providing that the innervation of these tissues was intact In the reviewer s opinion the data presented are not convincing mainly because adequate control was not exercised as to the effect of leakage of these potent chemical agents into the systemic circulation Moreover Heymans and his colleagues have repeatedly shown

that immediate circulatory or respiratory reflex responses do not occur when these drugs are injected into isolated areas of the peripheral circulation Acetylcholine cyanide and nicotine injected intravenously do not produce hyperpnœa if the aortic and carotid chemoreceptors have been denervated Kaufmann (1912) Odermatt (1923) Heymans Bouckaert Euler & Dautrebande (1932) also agreed that changes in oxygen or CO content in the arterial blood perfusing the isolated but innervated limbs did not induce reflex circulatory or respiratory responses High doses of irritating chemical stimulants may however induce reflex circulatory or respiratory reactions if injected into the arterial circulation but these reactions are most likely due not to stimulation of specific chemo receptors but to the stimulation of non specific pain receptors or other receptors as already shown by Heidenhain (1870) Bradford (1889) Tigerstedt (1923) and others

Section 3 Cardio-Pulmonary Reflexes

Chapter 22

ANATOMICAL AND ELECTROPHYSIOLOGICAL STUDIES ON THE CARDIO-PULMONARY NERVES

The Autonomic Innervation of the Heart and Pulmonary Vessels

The cardio pulmonary area is generously innervated by the vagal and sympathetic nerves The Weber brothers (1845) showed that stimulation of the vagus nerves caused bradycardia Though they attempted a rough localization of the cardiac vagal centre it was Laborde (1888) who first showed its situation in the floor of the IVth ventricle and Miller & Bowman (1915) later identified the centre with the dorsal motor nucleus of the vagus

Vierordt (1855) and later von Bezold (1863) and Cyon (1866 1867) reported that stimulation of the sympathetic caused cardiac acceleration The Cyon brothers (1867) found that stellatectomy abolished the response of tachycardia to the stimulation of the cervical part of the spinal cord Schmiedeberg (1871) was the first to demonstrate the course of the rami accelerantes

Since these papers from the Leipzig laboratory there has been a huge amount of work carried out on the anatomical pathways of the autonomic nerves supplying the cardio pulmonary area Tigerstedt s monograph may be consulted for some of the details of the cardiac innervation in mammalian and non mammalian forms (Tigerstedt 1921) Among the more important papers concerning the anatomy and histology those of Wooldridge (1883) Smirnow (1895) Dogiel (1898 1911) Ellenberger & Baum (1891) Cyon (1898 1900 1906) von Schumacher (1902) Dogiel & Archangelsky (1906) Worobiew (1917) Woollard (1926) Anufriew (1928) Schurawlew (1928) Wolhynski (1928) and Nonidez (1937 1939 1941 and 1943) may be mentioned Recently there has appeared an able account of the anatomy of the heart nerves of the dog by Mizeres (1955) Jarisch & Richter (1939) Amann & Schaefer (1943) Jarisch & Zotterman (1948) Dawes & Widdicombe (1953) and Jones (1952 1953) give some account of the pathways of some of the vagal afferent nerves whose cardiac nerve endings are stimulated by veratrine and its constituents

The older investigations were in the main conducted by the ordinary methods of anatomical dissection using the technique of methylene blue staining for following the finer branches Unless such studies comprise investigations made on survival animals in which supranodose vagotomy or stellatectomy has been carried out there is no certain way of deciding whether nerve fibre branches contain afferents or efferents or whether vagal branches contain sympathetic fibres and vice versa For this reason we consider that there is little point in presenting detailed maps of the anatomy of the cardiac nerves which may be consulted in the papers of Anufriew Schurawlew Wolhynski and Mizeres already referred to

Conventionally one describes three cardiosympathetic nerves on each side arising from the superior middle and inferior cervical ganglia and named accordingly Usually however there are additional rami which pass from the thoracic sympathetic trunk to the heart (Perman 1924 Cannon *et al* 1926 Ionescu & Enachescu 1928 Kuntz 1934 1945) The efferent components of the sympathetic nerves are postganglionic fibres which have their cell bodies in the sympathetic ganglia The corresponding preganglionic rami arise from the segments T_1–T_5 of the spinal cord By recording impulse activity in the post ganglionic neurones of the inferior cardiac sympathetic nerve Bronk (1933–34) was able to show the effect of successive section of the preganglionic rami in these segments on the impulse discharge Some of the most authoritative work on the distribution of the cardiac sympathetic nerves is that of Nonidez (1937 1939 1941 1943) based on the use of silver staining techniques Preganglionic sympathetic fibres stained deeply whereas the post ganglionic sympathetic fibres stained only a pale orange His description of the course of the cardiosympathetic and cardiovagal nerves is summarized below

The superior cardiosympathetic nerve is according to Nonidez mis named as it supplies only the large vessels On the left it arises from the medial surface of the middle cervical ganglion and is joined by aortic nerve fibres from the depressor nerve The branch consists of pale staining postganglionic sympathetic fibres (silver technique) and supplies the aortic arch and the base of the brachiocephalic Nonidez claims that the homologue of the right side is the aortic nerve ending on the base of the subclavian artery This seems highly unlikely

The middle cardiac sympathetic nerve (nervus accelerator of Boehm) is the largest branch issuing from the mid cervical ganglion On the left it arises from the caudal pole of the ganglion medial to the ventral limb of the ansa subclavia It runs lateral to and in close contact with the vagus into the thorax wherein it divides into branches which run ventrally over the aortic arch and left pulmonary artery to enter the plexus situated in the fold of epicardium containing the remnant of the left anterior cardinal vein (the plica nervina (Worobiew 1917) It is joined near the heart by parasympathetic cardiovagal fibres As the n accelerator reaches the base of the left ventricle the fibres course along coronary arterial branches which supply the left heart and terminate in the left posterior longitudinal plexus of Worobiew (1917) Branches of the accelerator accom panied by vagal fibres are also distributed to the posterior surface of the left atrium

On the right the nerve runs from the middle cervical ganglion and joins the right cardiovagal branch which causes the afferent fibres ending in the baroreceptor area at the base of the right subclavian At the angle of the subclavian the nerve courses in the mediastinum behind the aorta to reach the heart where it joins the left anterior longitudinal plexus and the right anterior and right posterior plexuses which innervate the right atrium and ventricle

The inferior cardiosympathetic nerves are not constant in the dog but when present join the nervus accelerator high or low in its course In the cat the right stellate ganglion gives several branches which join the right accelerator and run with it leaving this nerve in the vicinity of the angle of the right atrium and superior vena cava

The cardiovagal nerves are less numerous than those from the sympathetic The left cardiovagal nerve according to Nonidez arises from the vagus at the level of the mid cervical ganglion and runs to the pressoreceptor area on the ventral surface of the aorta

It contains afferent fibres from the aortic arch The right cardiovagal nerve joins the nervus accelerator in the dog In the cat it issues from the vagus at about the level of the tracheal bifurcation whence it runs to the posterior surface of the right atrium between the openings of the venæ cavæ In our experience and that of others this is a very constant branch in the cat and it can always be identified leaving the vagus only a few millimetres headward of the junction between the azygos vein and the superior vena cava then running medially behind the azygos vein and lymph node to the posterior surface and right side of the atrium

Histological methods have been profitably combined with experimental physiological studies in helping to decide the fibre components of the cardiac nerves (Heinbecker 1930 Heinbecker & O Leary 1933 Daly & Evans 1953) and Agostoni *et al* (1957) These authors have examined the functional and histological characteristics of the vagus and its branches after supranodose or infranodose vagotomy In chronic survival animals following supranodose vagotomy Heinbecker & O Leary found no effects on the heart rate on stimulating the cervical vagus trunk They concluded that none of the cell bodies of the cardiac motor fibres lay in the nodose ganglion Heinbecker (1930) showed that the compound vagus action potential contained three peaks and correlated these with fibre sizes in preparations stained with osmic acid He associated the first part of the first peak with the activity of large myelinated fibres which were of motor function for this part of the compound action potential disappeared after chronic supranodose vagotomy The second part of the first peak which survived supranodose vagotomy was identified with the activity of large myelinated afferent fibres The second wave was associated with small myelinated fibre activity and the third with that in non myelinated fibres Chronic supranodose vagotomy was found to reduce the second wave by some 30–50% in size which was in harmony with the disappearance of about half of the small finely myelinated fibres from histological sections It would seem that most of the finely myelinated fibres are afferent Heinbecker & O Leary decided that there were no non myelinated afferent fibres in the vagus of the cat because pressure applied to the vagal trunk which abolished the first two potential waves without affecting the third effectively blocked the reflex responses to impulses aroused by pain or by changes in the blood pressure and respiration

Daly & Evans (1953) did not agree with this last point They studied the results of chronic supranodose vagotomy on the histological features of the vagus and its thoracic branches and on the responses obtained by vagal stimulation Supranodose vagotomy had little effect on the larger myelinated fibres but caused a disappearance of 60% of the 2–4 μ myelinated group In the cardiac branches there was no obvious degeneration in the myelinated fibres but definite degeneration of some of the non myelinated fibres The large number of myelinated and non myelinated fibres which survived were afferent in function

Agostoni *et al* (1957) have extended these studies They report that the cardiac vagal branches contain in all about 3 000 fibres (cat) Only 500 fibres mostly non myelinated disappear after supranodose vagal section so the remainder are afferent About 500–700 fibres were myelinated these lay in the range 1–12 μ and were afferent 10% of the components of the vagal branches were sympathetic fibres

The Intrinsic Innervation of the Heart and Pulmonary Vessels

There is no general agreement regarding the number and distribution of nerve fibres and receptors in the various layers of the heart wall This is presumably due to technical difficulties in the histological techniques involved Kuntz (1934) regards the intra vitam methylene blue method as the most satisfactory although many have obtained good results with silver methods (e g Nonidez 1937 and Pannier 1940) Woollard found

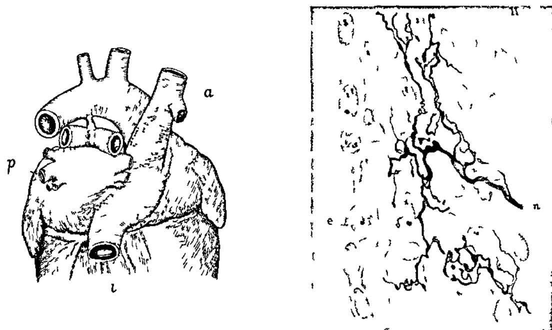


Fig 79*a* Posterior view of the heart of a kitten showing the location and approximate extent of the receptor areas of the veins (dotted) *a* = azygos vein opening into the superior vena cava *i* = inferior vena cava *p* = pulmonary veins
Fig 79*b* Receptors in the subendothelial layer of the vena cava at the atriocaval junction —(Nonidez J F (1937) *Amer J Anat* **61** 203)

numerous ganglia in the atrial walls but was unable to demonstrate any on the ventricular side of the atrio ventricular sulcus Anufriew (1928) and Schurawlew (1928) confirmed these findings Okamura (1930) claimed that ganglia existed in all parts of the cardiac wall Dogiel (1898*b*) described the neurons in the atrial cardiac ganglia in detail and divided them into three classes Probably all the extrinsic fibres which make synaptic connection with the ganglion cells are vagal according to Woollard (1926) and Lavrentiev (1929) The cardiac ganglia are therefore wholly parasympathetic Woollard found that the ventricular muscle was supplied only by sympathetic fibres

Sensory fibres from the heart were investigated first by Smirnow (1895) then by Dogiel (1898*a*) and have more recently received a good deal of attention Nonidez (1937) described a generous supply of subendothelial receptors on the dorso medial surface of the junction of the superior vena cava with the right atrium These were vagal nerve

endings Nonidez claimed that they were receptors for the Bainbridge reflex but more recent evidence suggests that this is unlikely

In addition to these subendothelial endings in the newborn kitten which he found in the venæ cavæ in their intrapericardial course, Nonidez also described similar nerve endings in the subendothelial part of the pulmonary veins encircling their circumference again in the intrapericardial part of the veins (see Fig 79) He also drew attention (1943) to the rich sensory innervation of the sino atrial node and a v node Pannier (1940) repeated these observations using silver techniques in the adult cat He found (1) sensory endings on the dorsal surface of the superior vena cava in the subendothelial part of the wall (2) endings in the subendothelium of the right pulmonary vein (Larsell 1921 Nonidez 1937 see also Lavrentiev 1946) (3) sensory endings of very thin fibres in the vicinity of the sino atrial node (4) fine reticulated vagal endings in the pulmonary artery sensory in type as previously described by Larsell & Dow (1933) Takino (1932) Takino & Miyake (1936) Takino & Watanabe (1938) and earlier by von Schumacher (1902) Lastly Pannier reported vagal receptors in the myocardium of the right auricle and atrium He considered that the atrial receptors were more likely to subserve the Jarisch reflex (Jarisch 1938–1941 Jarisch & Richter 1939*a b c*) than the Bainbridge reflex (Bainbridge 1915)

King (1939) injected methylene blue solution *in vivo* into rats finding that 10–20 ml could be injected before death occurred The heart was frozen *in toto* upon the microtome After a section was cut it was allowed to oxidize and was then fixed King described a variety of complicated forms of cardiac nerve endings These comprised (*a*) small encapsulated receptors The nerve fibre ended in a cylindrical whorl which was completely surrounded by a thin transparent capsule This type was found quite frequently in the ventricles lying between the muscle bundles A common location was between layers of muscle the fibres of which were running in different directions (*b*) Muscle spindles were demonstrated in the ventricles of varying degrees of complexity Very large endings situated within a thin capsule whose termination was composed of a complicated mass of nerve fibres and small strands of muscles were occasionally found Only a few endings of this type were observed in the ventricle and none was found in the atrium (*c*) A third type was similar to the last but was less complicated in structure This was commonly found in the ventricles and was not found in the atria

King regards these spindles found in cardiac muscle as being of a type transitional between those observed in striated and smooth muscle The stretch receptors in smooth muscle have no capsule whereas those in striated muscle are of great complexity and are usually covered by connective tissue The cardiac spindles sometimes have a thin capsule but occasionally possess no demonstrable sheath King considers the cardiac muscle spindles to be stretch receptors Except for this author only Plechkova (1936) has described sensory spindle like structures in cardiac muscle Nonidez (1943) has denied the existence of ventricular receptors

Electroneurography of Cardiac Vagal Afferent Nerves

Amann and Schaefer (1943) described the main features of the impulse traffic which may be recorded from the cut central end of the right cardiac vagal branches Bursts of impulses occurred synchronously with atrial and ventricular contraction (see Fig 80)

A single functional fibre was recorded which showed impulse activity in the P R interval of the ECG Amann and Schaefer considered that the large spike potentials which they recorded originated from the activation of nerve endings in the atria and the ventricles The afferent fibres were presumed to be of the A class (Erlanger & Gasser 1937) Jarisch & Zotterman (1948) however denied that mechanical stimulation of ventricular nerve

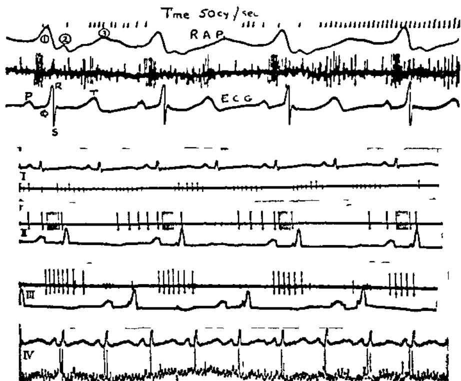


FIG 80*a* Records taken of impulse activity of a thin slip of the cardiac vagus (central end) Records from above downwards time 50 c/s right atrial pressure electroneurogram and E C G —(E Neil Zotterman (1950) *Acta physiol scand* 20 160)
FIG 80*b* I II III shows E C G and electroneurogram of three separate preparations of cardiac vagal afferents I shows B type atrial receptor (right atrium) II shows A typ atrial receptor (right atrium) III shows arterial baroreceptor from the aortic arch IV shows right ventricular receptor —(E Neil)

endings elicited any large spike potentials in the afferent cardiac vagal fibres Only atrial stimulation elicited these large potentials ventricular stimulation by pinching the ventricular wall caused the appearance of small slowly conducted spikes which they considered to be conducted in thin afferent fibres of the δ_2 or C type Jarisch & Zotterman drew attention to the great preponderance of myelinated and unmyelinated cardiac vagal fibres which were less than 1 5μ in diameter and pointed out that few fibres in these branches exceeded 3μ in diameter Electrical stimulation of the central ends of these cardiac vagal branches if effective at all caused only reflex bradycardia and hypotension Neil & Zotterman (1950) found that these reflex effects on the circulation were elicitable only if the electrical stimulation was sufficiently powerful to excite the δ fibre component

of the compound vagal action potential They concluded that reflex vagal bradycardia and hypotension was mediated by thin fibres of the δ or C type

Whitteridge (1948) recorded the impulse activity in few fibre preparations of cardiac vagal afferents made by dissecting the cervical vagus Simultaneous recording of pulse waves in the great veins, intrathoracic pressure aortic pressure and ECG allowed him to correlate the vagal impulse traffic with the effective venous pressure He found that bursts of impulses occurred synchronously with each of the a' c and v waves of venous pulse pressure Some of the nerve endings were situated in the left atrium even though the corresponding afferent fibres coursed in the right cervical vagus Cold block



FIG 81 Two records showing, E C G (upper record) single fibre of atrial stretch receptor (A type and single lung stretch receptor (lower record)
(a) During natural inspiration A receptor discharge increases and secondary firing is obvious in the venous filling phase At the end of inspiration (signalled by the cessation of discharge of the small spike of the lung stretch receptor) the A receptor discharge lessens
(b) During positive pressure inflation of lung the small spike discharge is very great the A receptor firing is reduced and there is no secondary firing due to the interference with venous filling As soon as the positive pressure is released venous filling occurs and causes secondary firing and increased discharge in the P R interval —(E Neil)

was applied to the cervical vagus and the venous receptor impulses were no longer conducted below a temperature which lay between 8 and 12°C The venous afferent fibres were found to be resistant to anoxia Whitteridge also claimed that a second type of nerve ending lay in the pulmonary vascular circuit The impulse traffic in the corresponding fibres appeared very late in systole some 200 msec after the *Q* wave of the ECG The following characteristics laid down by Whitteridge allow the recognition of these pulmonary vascular vagal receptors

(1) The a wave of the jugular venous pulse should not be accompanied by any impulse activity
(2) Activity characteristically late in systole should be markedly increased by increased venous return as produced by normal inspiration or by suction of air from the trachea Conversely positive pressure inflation of the lungs should cause a decrease in impulse activity of these vagal fibres (Fig 82)

Whitteridge also isolated fibres in which the electroneurogram showed a volley of impulses occurring at the very beginning of ventricular systole He tentatively identified these as arising from ventricular nerve endings which were stimulated by the use of ventricular

wall tension during the phase of isometric contraction Positive pressure inflation of the lungs increased the activity in these fibres

Dickinson (1950) Pearce (1951) Pearce & Whitteridge (1951) Pearce & Henry (1956) Coleridge *et al* (1956) and notably Paintal (1953–1955) have further investigated these problems

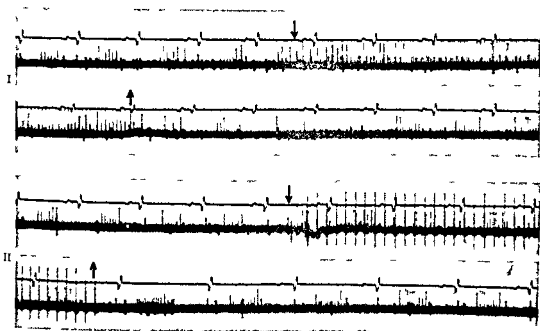


FIG 8 Two records I and II obtained from central end of cervical vagus slip which contains a single B type atrial receptor and a large Hering Breuer lung stretch receptor (lower record) and E C G (upper record)

FIG 82 I Between arrows positive pressure inflation of lung Note disappearance of B receptor discharge together with the intense discharge from the large Hering Breuer receptor On release of inflation note the rapid increase in discharge of the B receptor as the venous filling increases

FIG 82 II Between arrows the left peripheral vagus was stimulated (15 c/s) so as to slow the heart The stimulus artefact can be clearly seen as a large displacement in the electrical record Note that the B receptor fires more actively at the slower heart rate which occurs during and after the vagal stimulation —(E Neil)

Paintal (1953*a*) proved that the pulmonary vascular vagal nerve endings described by Whitteridge lay in the atria Isolation of single units which fulfilled the criteria given above was followed by anatomical localization of the corresponding nerve endings Paintal found that many of the receptors lay in the left atria as well as the right even though the nerve fibres he studied were all dissected from the right cervical vagus Atrial receptors of this type were located only in the posterior part of each atrium near the openings of the veins None was discovered in the appendages or near the inter atrial septum Impulse activity bore a linear relationship to atrial filling Paintal inferred that the nerve endings were stretch receptors activated by changes in atrial filling He designated them

type B atrial receptors in order to distinguish them from the A type (Fig 81) which show impulse activity invariably in the P–R interval of the ECG with secondary firing accompanying the *V* wave of the jugular or atrial pulse (Paintal 1953*b*) Whitteridge (1953) has suggested that A receptors lie in parallel and B receptors lie in series with the muscular elements of the cardiac wall A receptor fibres from the right atrium possess a mean conduction velocity of 20 m /sec (range 13–27) B receptor fibres of the right atrium have a mean conduction velocity of 13 m /sec (range 8–23) and those of the left atrium a mean conduction velocity of 20 m /sec (range 15–26) (Paintal 1953*c*) Paintal found a mean conduction velocity of 36 m /sec for pulmonary stretch receptors (range 14–59) and 33 m /sec for aortic baroreceptors (range 12–53) Hence a considerable overlap of conduction velocity exists in fibres subserving widely different sensory modalities Paintal believes that selective blocking of one type of afferent fibre by cooling the main vagal trunk is unlikely to be possible Figure 82 shows the effects of positive pressure inflation of the lung on the behaviour of a B receptor

Neither A nor B receptors showed any activation by veratrine or its constituents or by phenyl diguanide Pituitrin injected intravenously caused a five to ten fold increase in impulse activity of A and B receptor fibres entirely attributable to the raised pressure in both atria produced by systemic and pulmonary vasoconstriction (Paintal 1953*b*)

Paintal (1955*a*) has also shown that phenyl diguanide injected rapidly into the right atrium causes an activation within 0 9–2 7 sec of receptors which he located in the lung parenchyma in the vicinity of the alveoli Normally quiescent these receptors could be excited naturally only by rapid suction of air from the lungs He concluded from this that they were true pulmonary deflation receptors situated near the alveoli endings in such sites have been described (Berkley 1893 Okamura 1930 Miller 1950) His proof that they could be activated by phenyl diguanide that the corresponding fibres could be blocked by cooling to 3–4°C and that the fibres possess a conduction velocity of about 6 m /sec led him to suggest that these receptors were responsible for the pulmonary depressor reflex described by Dawes and his co workers (Dawes 1953)

Recently Paintal (1955*b*) has given a detailed description of the behaviour of ventricular pressure receptors which he found in both right and left ventricles These had previously been briefly mentioned by Whitteridge (1948) Dickinson (1950) and Pearce (1951) Isolation of single units by Paintal showed that they evinced an early systolic outburst of impulses within 20–60 msec after the *Q* wave of the ECG attaining a peak frequency about 25–70 msec after the *Q* wave The impulse activity was not affected by normal inspiration and in some cases was not even significantly affected by positive pressure inflation or negative pressure deflation From a comparison of the spike heights with those of other fibres Paintal concluded that the ventricular receptor fibres possessed a conduction velocity of 10–20 m /sec and belonged to the A class of sensory afferents The ventricular receptors were strongly stimulated by veratridine

The following reviews of the results of electrophysiological studies of cardiac afferents were written in the era which might be called Pre Paintal Dawes (1952*a* *b* 1953) Whitteridge (1953*a* *b*) and Schaefer (1950) Clearly the results of electrophysiology when coupled with the anatomical localization of the active receptors and subsequent histological confirmation are likely to be fruitful

CHAPTER 23

REFLEXES FROM THE HEART AND LUNG VESSELS

THE CLASSICAL technique of vascular isolation and perfusion used so successfully in the investigation of the carotid sinus reflexes is naturally much more difficult to apply in the case of study of the cardio pulmonary reflexes Nevertheless some results are available which indicate at least the qualitative nature of the reflex responses caused by raising the pressure in different parts of the cardio pulmonary circuit The quantitative responses have in general not been impressive but this may be attributed to the operative exposure inevitably required with consequent deterioration of the preparation

Reflexes from the Right Side of the Heart

Aviado *et al* (1951) have performed cross circulation experiments in which blood flowing in the right heart was isolated Blood returning via both venæ cavæ was collected and pumped into the right atrium whence it passed via the right ventricle to the pulmonary artery to be collected via a cannula This total pulmonary flow was pumped into a donor dog s veins for oxygenation and returned by a third pump to the recipient s left atrium A rise of perfusion pressure in the right heart caused bradycardia and hypotension The response no longer occurred after vagotomy Atropinization prevented the bradycardia caused by a rise of perfusion pressure The systemic hypotension was however still seen and therefore represented a reflex reduction in peripheral resistance The receptors concerned lay in the atria but not in the ventricle

Aviado *et al* (1951) found no consistent changes of respiration on raising the right heart pressure This is interesting because Megibow Katz & Feinstein (1943) reported fast deep breathing (abolished by vagotomy) on stretching the atrium or the atrio caval orifice by means of a cannula fitted with an umbrella rib device It is possible as noted elsewhere that such an instrument causes also distortion of structures in anatomical proximity to the atrium Harrison Harrison & Marsh (1932) also noted that atrial distension caused reflex hyperpnœa

Reflexes from the Pulmonary Vessels

Perfusion Studies

Churchill & Cope (1929) using cats ligated the vessels of one lung and having cannulated the corresponding pulmonary artery raised the static pressure in the vessels Bradycardia and hypotension resulted Respiration was affected inconsistently but tachypnœa often occurred Schwiegk (1935) obtained the same results in similar experiments on dogs and proved that the effects were reflex and were dependent on the integrity of the vagi The threshold value of change of static pulmonary pressure required to cause

a fall of systemic pressure was 10 mm Hg The reduction in heart rate per 10 mm Hg rise of pressure in the pulmonary vessels varied from 10–24 beats per minute Schweitzer (1936) obtained similar results in the cat in only two out of twelve animals He used static pulmonary pressures which were inordinately high compared with the normal mean pulmonary arterial pressures as later did Parin (1947)

These earlier results were obtained in preparations in which the rise of static pressure affected arteries capillaries and veins of the pulmonary circuit Aviado *et al* (1951) employed the technique already described which permitted a more discriminative study By suitable adjustment of the outflow cannula in the pulmonary artery the pulmonary arterial bifurcation could be included or excluded from the perfusion circuit By shunting the inflow from the first pump into the pulmonary trunk the right atrium and ventricle could be excluded and the pulmonary trunk pressure could thus be increased alone They claimed that a rise of pulmonary arterial pressure induced a vagal reflex bradycardia (but not hypotension) They gave no experimental record which substantiates this claim Indeed the one figure in their paper which is relevant to this point (Fig 5C) shows convincingly that a rise of right heart plus pulmonary perfusion pressure which is associated with a more prominent increase in pulmonary trunk pressure than in right auricular pressure caused no change in heart rate

With the exception of these claims of Aviado *et al* (1951) there is no direct evidence that the pulmonary trunk or pulmonary artery is necessarily the site of receptors which initiate cardiovascular reflexes of this type Guyton *et al* (1954) claim on inadequate evidence that pulmonary arterial baroreceptors exert a significant tonic reflex inhibitory effect on the vasomotor centre

On the other hand there is a steady accumulation of evidence that the pulmonary veins possess a sensory innervation which represents the end of the afferent arm of cardiovascular and respiratory reflexes Daly Ludany Todd & Verney (1937) separately perfused the systemic and pulmonary circulations in dogs They compared the effects of a rise in pulmonary arterial pressure produced by increasing the pulmonary flow with those of a *similar rise in p a p brought about by raising the pulmonary venous pressure* The rise of pulmonary venous pressure was effected by restricting the left atrial outflow Restriction of the left atrial outflow was more effective than was raised pulmonary flow in producing slight but definite reflex systemic hypotension On cutting the vagi all systemic responses disappeared As they were careful to point out their technique did not allow them to specify whether the receptors stimulated lay in the pulmonary veins or in the left atrium or in both In one experiment cocainization of the left atrial surface including the origin of the pulmonary veins did not abolish the reflex effects of restricting the left atrial outflow They did not regard this result as decisive owing to the difficulty of access to the posterior atrial surface They drew attention to the results of histological studies of Takino (1932) which suggest that the nerve supply to the pulmonary veins is a continuation of that to the left atrium (see also Nonidez 1937 Boyd 1952) Daly *et al* suggested that the fall of systemic pressure reflexly induced by the stretching of vascular receptors in the pulmonary veins and left atrium might be significant in connection with impaired functional activity of the left heart

Aviado *et al* (1951) pumped blood drawn from the right atrium of a donor dog through the cannulated left pulmonary artery of a recipient the outflow from the

recipient's left pulmonary vein being returned to the jugular vein of the donor The systemic circulation and pulmonary gaseous exchange of the recipient was maintained by his own heart and his other lung The chest was closed and after reduction of the pneumothorax spontaneous breathing was restored A rise of perfusion pressure in the pulmonary circuit was ineffective unless the pulmonary vein was also clamped thereby causing a rise of pulmonary venous pressure which in turn induced reflex systemic hypotension (but not bradycardia) and rapid shallow respiration with no increase in the pulmonary ventilation volume per minute If the perfusion were reversed by connecting

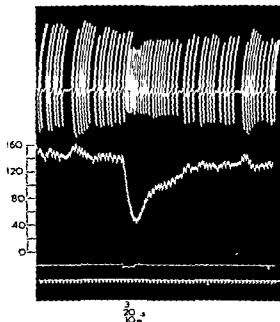


FIG 83 Cat Central end of right cardiac vagal branch placed on shielded electrodes pushed through the chest Chest closed pneumothorax reduced spontaneous respiration Records from above downwards respiration blood pressure signal and time in 5 second intervals At the signal electrical stimulation (3 v 20 c/s 10 ms) of central end of vagal branch Note tachypnœa hypotension and bradycardia —(F G Brewin and E Neil)

the pump inflow to the pulmonary vein and collecting the outflow from the pulmonary artery, an increased flow readily caused a rise of pulmonary venous pressure which again induced reflex systemic hypotension and tachypnœa The receptors concerned were therefore considered to lie in the pulmonary veins

It must be remembered that Churchill & Cope (1929) obtained reflex tachypnœa in their experiments in which they produced engorgement of the pulmonary vessels in a lung completely isolated from the body save for its nerves They clamped the artery and the vein to this isolated lung and injected fluid into the pulmonary artery whereupon tachypnœa occurred which was only terminated when the injected fluid was withdrawn Their results were corroborated by those of Harrison Calhoun *et al* (1932) who found that the tachypnœic response was dependent upon there being an intact vagal innervation Daly *et al* (1937) also showed that tachypnœa occurred in some of their experiments in which they increased the pulmonary inflow and suggested that the effect was mediated via vagal sensory receptors in the venous tree or in the capillaries

Some unpublished results of the present author may be cited in this respect In cats the most obvious cardiovagal branch on the right arises from the vagal trunk just

above the junction of the vena azygos with the superior vena cava This nerve was exposed by a third intercostal incision the nerve was cleared by dissection up to the point *where it runs along the postero lateral border of the right atrium The nerve was cut on* the surface of the heart and the two cm length thus obtained was secured to shielded electrodes which were passed through a puncture wound in the right first intercostal space Stimulation of the central end of this nerve caused bradycardia and hypotension in cats with open chests If the chest was shut however and the pneumothorax reduced so that the animals breathed spontaneously electrical stimulation of the nerve caused tachypnœa

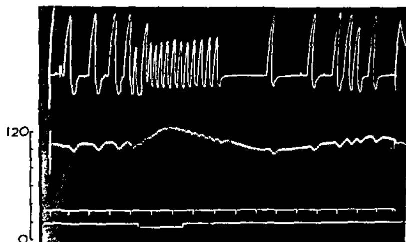


FIG 84 Procedure and arrangement as in previous figure but the central end of a thin component form the cardio vagal nerve (arising apparently from the pulmonary vein) was stimulated Note that stimulation (3 v 20 c/s 10 ms) causes conspicuous tachypnœa but slight hypertension with no bradycardia (see text) —(E. G Brewin and E Neil)

together with bradycardia and hypotension (Fig 83) Over the course of an hour or so the respiratory response to stimulation usually disappeared although those of bradycardia and hypotension remained about the same This suggested that the afferent fibres responsible for tachypnœa were different from those which caused the circulatory responses In further experiments the peripheral course of this nerve was followed In general it was found that the nerve gave off a fine branch to the pulmonary veins as it lay on the dorso lateral aspect of the heart On only one occasion this fine branch was itself stimulated in an animal with the chest reclosed The reflex response was tachypnœa without there being any evidence of hypotension or bradycardia (Fig 84)

The nerve stimulated was followed for perhaps a centimetre along the pulmonary vein—using 20 × magnification It was cut at a point at which it seemed to disappear into the adventitia of the vein This experimental result is not incompatible with the evidence advanced by Aviado *et al* that pulmonary venous receptors may form the afferent mechanism for reflex tachypnœa On the other hand we cannot prove that the nerve stimulated arose from the pulmonary vein itself and not from the smaller vessels of the pulmonary circuit

To summarize the evidence provided by classical perfusion methods suggests that the pulmonary vessels may be the site of receptors which when stimulated by a rise of mean pressure in the pulmonary circuit initiate cardiovascular and respiratory reflexes The quantitative responses have been disappointing but this may be due to the extent and duration of the operative exposure which causes deterioration of the condition of the beast Further evidence of cardiovascular and respiratory reflexes arising from the pulmonary circuit has been obtained by Dawes and his colleagues using drugs which excite nerve endings in this vicinity they have shown that marked depressor reflexes affecting the circulation can be induced by this means In addition there has been a long standing interest in the phenomenon of reflex tachypnœa first noted by Shaw Dunn to be the result of multiple embolization of the small lung vessels In each of these studies electrophysiological methods used by Paintal have given important information as to the characteristics of the receptors responsible We will therefore discuss the pulmonary depressor reflex initiated by the injection of amidine drugs followed by the reflexes evoked by multiple embolization of the lung

The Pulmonary Depressor Chemoreflex and the Pulmonary Respiratory Chemoreflex

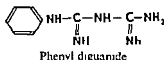
Brodie & Russell (1900) found that electrical stimulation of the central ends of the pulmonary vagi caused profound bradycardia and hypotension They concluded that these effects were reflex but their interpretation was later contested by Anrep Pascual & Rossler (1936) Anrep *et al* showed that some of the cardiac efferent vagal fibres ran into the pulmonary vagal branches and coursed downwards therein for an appreciable distance before looping to return in the same branches to the vagal trunk thence to be distributed via the cardiac vagal branches to the heart Anrep found that bradycardia could still be induced by stimulation of the central end of the pulmonary vagus after bilateral cervical vagotomy von Saalfeld (1932–33) obtained similar results

However Brodie (1900) also observed that the intravenous injection of serum or egg white into cats caused bradycardia and hypotension provided that the vagal branches to the lungs were intact He attributed these reflex effects to the stimulation of receptors in the pulmonary circulation Dawes & Feldberg (1948) demonstrated that the injection of 0 05 ml of horse serum directly into the left coronary artery produced a reflex brady cardia by causing stimulation of receptors in the vascular field supplied by the coronary arteries When injections of the same amounts of serum were made alternatively into the right and left atria bradycardia supervened earlier on injection into the left atrium but the effect was not so marked as that evoked by an injection into the right atrium Hence part at least of the reflex effect must have originated from receptors in the pulmonary vascular bed

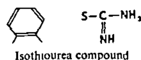
Dawes (1952*a* *b* 1953) and his co workers Dawes & Fastier (1950) Dawes *et al* (1951*a* *b* 1952) Barer & Nusser (1953) further examined the nature of reflexes induced by the stimulation of receptors in the lungs In testing substances which liberate histamine Paton (McIntosh & Paton 1949) noted that certain diguanides caused effects which superficially resembled those of substances which produced the Bezold reflex i e a fall of blood pressure and heart rate which no longer occurred after cutting the vagi Dawes & Mott (1950) investigated the action of these substances (which included phenyl diguanide

and phenyl guanidine) and confirmed that they caused marked hypotension and bradycardia together with a transient inhibition of respiration providing that the vagi were intact Analysis showed however that these responses were the result of three reflexes (1) bradycardia and hypotension due to the stimulation of cardiac receptors (evocable by injection of the drugs directly into the left coronary artery) (2) bradycardia and hypotension due to the stimulation of receptors in the lungs (3) inhibition of respiration due to the stimulation of receptors in the lungs The intravenous injection of as little as 50–100 μg phenyl diguanide induced bradycardia hypotension and apnœa The drugs were extremely specific in exciting these particular cardiovascular and respiratory reflexes The response to injection of the drug into the right atrium was usually greater and was often considerably greater than that which ensued upon the injection of the same dose into the left atrium A similar result was obtained when phenyl diguanide was injected directly into the pulmonary artery which indicated that there were receptors in the lungs which were stimulated by the drug

Dawes & Fastier (1950) continued the investigation by examining the reflex responses evoked by a series of amidine derivatives of the isothiourea type Dawes & Mott (1950) had found that diguanide derivatives were very active but had also noted that several aryl guanidines and amidines possessed appreciable activity As this suggested that the aliphatic side chain of phenyl diguanide could be modified considerably without total loss of activity the isothioureas were tested



Phenyl diguanide



Isothiourea compound

The most active of these isothioureas was the hydrobromide of 2 α naphthylethyl isothiourea In doses of 10–30 μg /kg given intravenously this was as effective in evoking the pulmonary vascular chemoreflex as was an intravenous injection of 100 μg phenyl diguanide The isothiourea compounds possessed the ability to initiate the three reflexes evoked by phenyl diguanide and phenyl guanidine although their reflex effect on respiration was more powerful than was their effect on the cardiovascular system Thirty to forty compounds of fairly simple structure all containing one amidine group $—C(\overset{+}{N}H_2)NH$ elicited these reflexes in the cat Nearly all the potent chemical relatives of phenyl diguanide possessed the structure aromatic nucleus—short side chain—unsubstituted amidine group Dawes & Fastier discussed the possibility that such compounds might owe their pharmacological activity to a chemical resemblance to some substance of physiological importance occurring naturally in the body

Dawes Mott & Widdicombe (1951*a* *b* 1952) made a more detailed study of the effects of phenyl-diguanide and 2 α naphthylethyl isothiourea in the cat and the rabbit Their most notable findings can be conveniently summarized

(1) The reflex bradycardia and hypotension was ascribed partly to the stimulation of vagal receptors in the heart itself supplied by the coronary circulation and partly to the stimulation of vagal receptors in the lung bed Cooling the cervical vagi to temperatures below 11°C did not abolish the reflex responses to these drugs although the responses were certainly reduced Complete abolition of the reflex responses

was only effected by cooling the vagi to temperatures as low as 3°C The coronary chemoreflex (Dawes & Comroe 1954) evoked by the stimulation of left ventricular receptors by veratridine was abolished by cooling the vagi to 9°–11°C The reduction of the reflex responses to the injection of the amidines by cooling the vagi to 11°C was therefore explained by there being a removal of some reflex effects normally exerted by the stimulation of cardiac receptors responsible for the coronary chemo reflex The persistence of considerable reflex responses to amidine injection during further cooling of the vagi to temperatures of 3°C indicated that these drugs also stimulated other receptors whose axons were of very small diameter The pul monary and left ventricular circulation time (Dawes & Comroe 1954) has since been shown to be 3–4 seconds This period which measures the time taken for blood to pass from the right ventricle to the ascending aorta in the cat is very similar to the latency (injection reflex time) between the injection of the amidines into the right atrium and the onset of reflex bradycardia This coincidence is again compatible with the conclusion that the amidines excite receptors in the lungs

(2) No thoracic vagal receptors could be found in electrophysiological studies which were excited by the amidines (Paintal (1953*b*) then confirmed this)

(3) Both phenyl diguanide and 2 α-naphthylethyl isothiourea evoked respiratory reflexes by exciting pulmonary receptors Transient apnœa followed by rapid shallow breath ing was the most frequent pattern of response seen in the cat These respiratory effects were likewise dependent on the vagi and survived cooling of these nerves until temperatures of 3-4 C were reached

Dawes *et al* believed that the amidines excited two different types of receptors in initiating the cardiovascular and respiratory responses respectively Thus the two responses could be dissociated by selective cooling of the vagi Moreover various active amidine compounds differed considerably in their ability to evoke the two types of reflex response

Comroe Van Lingen Stroud and Roncoroni (1953) found that 5 hydroxytryptamine injected into the right ventricle evoked a variety of circulatory and respiratory responses some of which were attributable to the stimulation of receptors situated between the site of injection and the coronary circulation i e in the lung bed Thus apnœa and brady cardia occurred within 3 seconds of the injection However hypotension which occurred was due to the bradycardia and did not occur with regularity when the cardiac slowing was prevented by atropine 5 HT occurs naturally in the body being present in the enterochromaffin cells of the gastro intestinal mucosa (Vialli & Erspamer 1933 Erspamer & Asero 1952) These cells are believed by Erspamer (1954) to release 5 HT into the blood from which it is selectively absorbed by the thrombocytes (Toh 1954) which act as circulating reservoirs of the substance Fastier (1955) has recently suggested that the activity of amidines in stimulating the pulmonary depressor chemoreflex increases as their structure approximates more nearly to that of 5 HT Thus phenyl diguanide S-1-(3-phenyl-)n-propyl isothiourea and 2-phenylethyl guanidine are almost equally potent in this respect and are considerably more active than homologues with shorter side chains However he admits that the inactivity of tryptamine itself is in conflict with this hypothesis (see also Fastier Waal & Wong (1957) Schneider & Yonkman (1953) Walker *et al* (1952 1953))

In small vessel embolization in the pulmonary circulation it has been suggested that the reflex systemic hypotension accompanied by bradycardia may be due to the clotting of blood around the foreign material with the subsequent local liberation of 5 HT from the platelets Such a change in the 5 HT concentration in the pulmonary bed may sensitize or stimulate the receptors of the pulmonary depressor chemoreflex

Paintal (1955*a*) has proved that pulmonary vagal deflation receptors (whose fibres are of small diameter) are stimulated by phenyl diguanide or by 5 HT with an injection response time of 1 1–2 7 seconds following the injection of these drugs into the right atrium This agrees fairly well with the injection reflex time of 1 7–4 3 seconds for bradycardia which is the rule in these circumstances The small diameter and slow con duction velocity of these fibres Paintal infers from their low spike height (Fig 85) and from the great difficulty he experienced in their isolation No other vagal afferents in the cardio pulmonary area have been shown to be excited by the amidines (phenyl diguanide) although gastric receptors had been thus activated (Paintal 1954) Neverthe less it is by no means proven that stimulation of these pulmonary deflation receptors is the sole cause of the pulmonary depressor reflex Prior to Paintal s findings (1955) Dawes & Comroe (1954) suggested that the pulmonary depressor reflex may cause a transference of blood from the pulmonary bed to the systemic circulation when a dangerous level of pulmonary hypertension is reached This would imply that the nerve endings affected would be stretch or pressoreceptors in the pulmonary bed Sparse evidence of the existence of such receptors exists from electrophysiological experiments (Swan & Whitteridge (1956)) Some depressor reflex effects have admittedly been induced by raising the perfusion pressure in the lung (Schwiegk 1935) but these have been much more feeble than those evoked by chemical stimulation by the amidines Moreover Paintal (1955*a*) noted that vascular congestion of the lungs caused considerable sensitiza tion of the pulmonary deflation receptors which is not incompatible with these receptors themselves playing a role in the circumstances envisaged by Dawes & Comroe (1954) Paintal considers that the excitation of the pulmonary deflation receptors by the amidines is responsible for both the pulmonary depressor and pulmonary respiratory chemo reflexes This is contrary to the opinion expressed earlier by Dawes *et al* (1951) However Paintal has argued that the reflex respiratory response to the amidines is stronger than is that of bradycardia Progressive cooling may thus lead to an apparent dissociation of the two reflexes merely because a greater number of conducting afferent fibres is required for the response of bradycardia than for the respiratory effects Certainly the similarity between the injection response time of the deflation receptors (1 9 sec) and the injection respiratory reflex time is striking Moreover the pulmonary deflation receptors respond briskly to the injection of phenyl diguanide 5 HT starch grains and nicotine all of which arouse the pulmonary respiratory reflex

Reflexes Initiated from the Smaller Vessels of the Pulmonary Circuit Arterioles, Capillaries and Venules

Multiple Minute Embolism and its Sequelae Shaw Dunn (1919) injected suspensions of starch grains intravenously in goats most of which were unanæsthetized some were anæsthetized with urethane The characteristic response to a dose of 3–4 g starch was

tachypnœa The breathing rate sometimes increased as much as fourfold The respiratory volume was sometimes unchanged but with the faster rates seen occasionally rose The depth of each breath was reduced The reaction continued for some hours before the animals died Cardiac output was measured by the direct application of Fick s principle blood being withdrawn from the right ventricle by a needle pushed through the chest wall

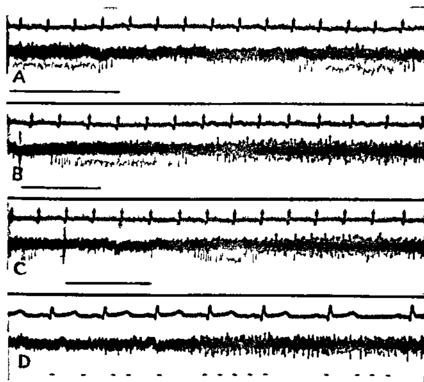


FIG 85 Action of HT on deflation receptors 2 5 ml saline 175µg phenyl diguanide and 75µg HT were injected in A B and C respectively Activity is produced in deflation fibres in B and C the pulmonary stretch fibre downward monophasic spike is unaffected D shows the response in another strand following injection of 20µg HT (6µg /kg) into the right atrium Slowing of the heart is clearly seen in B and D —(A S Paintal (1955a) *Quart J exp Physiol* 40 89)

Cardiac output blood pressure and venous pressure showed inconspicuous changes and were obviously not responsible for the tachypnœa Arterial blood samples showed no change in oxygen saturation when withdrawn in the early stages although gross anoxæmia was the rule in the later phases Alkali reserve was normal in the early blood samples and the tachypnœa was not due to CO retention Indeed the inhalation of 5 % CO_2 in air caused a deepening and slowing of the breathing The pulmonary arterial pressure was stated to be normal Dunn found that the tachypnœa was abolished by cutting the vagi and as he was unable to find any respiratory or cardiovascular cause for the rapid breathing of multiple embolization concluded that the effect was reflex being mediated by vagal afferents

Binger and his colleagues (1924 1927) later thoroughly investigated multiple minute embolism in dogs They drew attention to the fact that vagotomy abolished hyperpnœa even when it was of central origin In the present context however, we are more interested in the nervous factors concerned with embolic tachypnœa than in their detailed findings Christie (1938) suggested that sensitization of the stretch receptors of the lung was responsible for dyspnœa and at his instigation Partridge (1935) examined the effect of starch embolization on these receptors She concluded that they were sensitized but Walsh (1947) did not confirm this Bulbring & Whitteridge (1945) could find no evidence of any increase in sensitivity of the Hering Breuer receptors in experimental congestion Megibow Katz & Steinitz (1942) and Megibow Katz & Feinstein (1943) using a London cannula for recording the pulmonary arterial pressure in unanæsthetized dogs studied the respiratory and cardiovascular effects of a 1 20 suspension of starch granules Tachypnœa unaccompanied by hyperpnœa or dyspnœa occurred in each of sixteen experiments Like Binger and his colleagues and Shaw Dunn they could not relate this to anoxæmia or hypercapnia in the early stages following embolization

The pulmonary arterial pressure and respiration were recorded simultaneously in four animals pulmonary hypertension occurred first upon which tachypnœa developed Once tachypnœa became manifest it gradually progressed in intensity and at the same time the pulmonary arterial pressure rose Megibow *et al* related the tachypnœa to the obstruction with its associated congestion behind the obstruction They did not believe the tachypnœa to be due to local irritation by the starch granules acting as foreign bodies since if this were the case no aggravation of tachypnœa with time should occur This progression with time and the associated rise in pulmonary pressure appeared to be due to the development of antemortem clots around the starch granules demonstrable at post mortem examination Dawes & Comroe (1954) have since referred to the possible liberation of 5 hydroxytryptamine from platelets which break up round foreign emboli 5 HT is not only a vasoconstrictor but also stimulates pulmonary deflation receptors which Paintal (1955) believes are the afferent endings of the pulmonary depressor and pulmonary respiratory reflexes Megibow *et al* concluded that the smaller branches of the pulmonary arteries were obstructed by the emboli and that the distension so produced initiated a reflex from receptors in such vessels

Whitteridge (1950) reviewing multiple embolism of the lung refers to potato starch grains as being from 10–100μ in diameter and wheat starch grains as from 5–25μ Megibow *et al* did not specify the source of their starch However it seems likely that the starch grains would lodge mainly in the arterioles and pre capillaries perhaps even in the capillaries Torrance & Whitteridge (1947) showed that the tachypnœa of multiple minute pulmonary embolism persisted until the cervical vagi were cooled below 6°C This would suggest that the afferent fibres are of moderate size Whitteridge agreed with Megibow *et al* that it was difficult to explain the phenomenon unless one assumed the presence of afferent nerve endings in the pulmonary arterioles or precapillaries Some histological evidence exists for such receptors (Dogiel 1898 Karsner 1911 Takino 1932) but Elftmann (1943) found none It is possible that endings lying in the arterioles cause reflex pulmonary vasoconstriction when they are stimulated Their normal function might be to keep the pulmonary capillary pressure below levels at which œdema of the lung would occur If an embolus lodged in the precapillary then such an ending would

be stimulated and the reflex vasoconstriction so produced would tend to increase its stimulation The resultant situation might well explain the catastrophic nature of the reactions produced (Whitteridge)

Papaverine 32-64 mg given intravenously by Megibow *et al* to dogs with embolic tachypnœa produced a marked slowing of respiration which lasted up to ten minutes or more in some cases The drug was much less effective in dogs with moderate or major sized emboli These results support the view that the tachypnœa of minute embolization is a reflex phenomenon caused by distention of small vessels

Two further contributions throw some light on this subject Paintal (1955*a*) has shown that pulmonary deflation receptors are stimulated following the intravenous injection of potato starch suspensions and suggests that these receptors are at least partly concerned with the production of tachypnœa in these circumstances The initial respiratory inhibition following a rapid injection of starch grains could be explained by the sudden outburst of impulses in the deflation fibres whereas the tachypnœa which ensues might be due to a more moderate increase in activity of these fibres The pulmonary deflation receptors are sensitized by pulmonary congestion and hence the reflex tachypnœa is likely to be sustained if such congestion occurs The size and conduction velocity of the deflation receptor fibres are small and the above findings or inferences are not incompatible with the demonstration that the reflex tachypnœa of starch embolization survives cooling of the cervical vagi to temperatures of 6°C Paintal does not claim that the pulmonary deflation receptors are solely responsible for the reflex responses and points out that pulmonary arterial receptors noted by Swan & Whitteridge (1956) may be also concerned As we have seen the pulmonary deflation receptors are stimulated by 5 hydroxytryptamine which is carried in the thrombocytes this may be of importance in pulmonary embolization for clotting of the blood must usually occur round the foreign material with subsequent liberation of 5 HT in intimate contact perhaps with sensory receptors of the pulmonary depressor and respiratory chemoreflexes (Comroe *et al* 1953 Dawes & Comroe 1954) As Paintal has suggested that the pulmonary deflation receptors are concerned in both these reflexes it is interesting that some of the effects at least of multiple embolization can simulate those produced in the pulmonary depressor and respiratory chemoreflexes

Niden & Aviado (1956) have recently shown that multiple embolization of the lung vessels by glass beads (60–420 micra) injected into the right ventricle of dogs caused an immediate bradycardia and apnœa followed later by tachypnœa The respiratory and cardiac effects were shown to be of vagal origin Pulmonary hypertension which occurred was at least partly due to changes in the vascular resistance of the lung vessels as was shown by perfusing the lower lobe of the left lung by means of a pump which supplied a constant volume flow of blood from the right atrium of a donor dog Three components in the response to pulmonary embolization were revealed (1) primary mechanical obstruction which produced an immediate rise in pulmonary arterial pressure (2) secondary local vasoconstriction as shown by the further rise in pressure only when beads of less than 250 micra diameter were injected and (3) vasoconstriction extending to the other lobes This interlobar vasoconstriction was shown to be partly mediated by the vagi According to the authors anoxemia contributed to the stimulation of depth of breathing produced by emboli which still occurred after vagotomy in their experiments The perfused lung

technique revealed the presence of arterio venous shunts at least 420 micra in diameter These a v communications were opened when a rise in pulmonary arterial pressure occurred and were closed or narrowed by ventilating the lung with pure oxygen Niden & Aviado suggest that the shunts may be opened following pulmonary embolism thereby minimizing the rise in pulmonary arterial pressure though at the same time necessarily aggravating the degree of systemic anoxæmia

There is no evidence that the stimulation of pulmonary deflation receptors causes interlobar vascular constriction in the pulmonary circuit Here again it is possible that vagal receptors in the pulmonary arterioles may be responsible for such effects Likewise there is no evidence that the patency of pulmonary a v shunts is determined by nervous factors More work is needed here

Initiation of Pulmonary Vasoconstriction by Reflexes from the Pulmonary Vascular Receptors

These claims of the initiation of pulmonary vasoconstriction by the stimulation of receptors in the lung vessels themselves deserve some additional attention owing to recent developments in clinical research Before considering these results we might pause briefly to note that the pulmonary arteries receive a rich innervation from the sympathetic nervous system (Karsner 1911 Larsell 1921) It is largely due to the work of I de Burgh Daly (1933 1935–6) and his school (Daly *et al* 1942 1952 Daly & von Euler, 1932 Daly & Hebb 1952) that we have clear proof that the sympathetic innervation of the pulmonary vessels is predominantly vasoconstrictor Daly *et al* (1952) found that the stimulation of the upper sympathetic outflow (cranial end of the cut upper thoracic sympathetic chain sectioned between the third and fourth thoracic ganglia or the stellate or middle cervical ganglia occasionally reduced the lung blood flow by some 30% It is true as Folkow (1955) has pointed out that sympathetic discharge to the systemic vessels causes a much greater degree of constriction than this but if the lung vessels are regarded as part of the reservoir system of the circulation such vasoconstriction may be of considerable importance in circulatory adjustments Whitteridge (1950) has referred to the widespread belief that changes in pulmonary vascular resistance passively follow changes in lung volume This he believes is an over simplification of the statement of Hamilton *et al* (1939) that we can find no evidence that vasoconstriction of the pulmonary bed plays any significant role in the pulmonary hæmodynamics Nevertheless it seems from the results of more recent work that pulmonary vasoconstriction can be reflexly initiated in both experimental and clinical conditions

Sternberg & Tamari (1928) injected Indian ink suspensions into unanæsthetized rabbits which promptly died On post mortem examination the carbon granule impaction was confined to the precapillary vessels If the animals were anæsthetized similar injections were not lethal and on post mortem the carbon granules were uniformly distributed throughout the lung vessels These results suggest that the vessels of the lung possess some degree of tonic neurogenic vasoconstriction

The clinical evidence of pulmonary vasoconstriction of reflex origin derives from the work of Dexter and his collaborators (Hellems *et al* 1948 1949 Dexter *et al* 1950*a b* Dexter 1952) and from results of Fowler *et al* (1950) and Greene & Bunnell (1950) Hellems Haynes Dexter & Kinney (1948) introduced the technique of measuring

pulmonary capillary pressure by passing a catheter via the right heart into the pulmonary artery and thence distally until the catheter tip wedged in and occluded the distal branch The size of the vessel so occluded was usually of the order of 2–3 mm The pressure so measured was about 2 mm Hg less than the true capillary pressure in the dog Aspiration of blood through the catheter allowed the withdrawal of samples whose oxygenation was almost complete By the use of a double bore catheter pulmonary arterial pressure could be measured simultaneously by removing blood from the pulmonary artery and a systemic artery during the collection of the expired air of the subject the cardiac output could be determined using the direct Fick method Pulmonary arteriolar resistance was calculated as —

$$R = \frac{PA_m - PC_m}{Q/_t} \times 1332$$

Where R is the resistance in dynes seconds cm $^{-5}$ PA_m and PC_m are the mean pulmonary artery and capillary pressures respectively in mm Hg and $Q/_t$ is the cardiac output in ml /sec 1332 is the usual conversion factor from mm Hg to dynes/cm

Thus supposing the mean pulmonary arterial pressure is 15 mm Hg and the mean capillary pressure is 9 mm Hg then with a cardiac output of 125 ml /sec the pulmonary arteriolar resistance is about 67 dynes seconds cm $^{-5}$

Burton (1953) has strongly criticized the use of the term pulmonary capillary pressure pointing out that it would be better to express it as the impacted small artery pressure as this may vary considerably On the other hand Hellems Haynes & Dexter (1949) studied two patients with atrial septal defect and wedged the catheter first in the pulmonary vein and then in the pulmonary artery The pressures measured in these two sites were identical Bjork and his colleagues (1954) have simultaneously recorded the pulmonary capillary pressure and the pressure in the left atrium obtaining the latter by his paravertebral puncture method The two pressure curves showed remarkably good coincidence in most cases during normal resting conditions and were very similarly affected by changes of intrathoracic pressure caused by the Valsalva manœuvre

Dexter and his co workers (1950*a* *b* 1952) have investigated the changes in pulmonary arteriolar resistance in a variety of clinical conditions—notably in patients suffering from mitral disease or from congenital heart disease In patients with mitral stenosis they found the pulmonary capillary pressure raised but noted that the pulmonary arteriolar resistance was sensibly normal unless the pulmonary capillary pressure approached that of the osmotic pressure of the plasma proteins i e 25 mm Hg If the pressure in the pulmonary capillaries reached 20 mm or so there was usually a marked rise in the pulmonary arterial pressure which in turn was ascribed to an increase in the pulmonary arteriolar vascular resistance according to Westcott *et al* (1951) this sudden increase in resistance may be due to anoxia In some cases of severe mitral stenosis pulmonary arteriolar vascular resistance approached that calculable in the systemic circulation They tentatively suggest (Dexter *et al* 1950) that this increase of pulmonary arteriolar resistance is due to active vasoconstriction which they consider may be regarded as compensatory in nature serving to protect the pulmonary capillaries from a high hydrostatic pressure and pulmonary œdema Now it is likely that a part of the increased pulmonary arteriolar resistance in mitral stenosis is due to muscular hypertrophy and intimal hyperplasia which

occurs in these cases (Moschkowitz 1927, Parker & Weiss 1936 Larrabee Parker & Edwards 1949) Henry (1952) has recently described diffuse muscularization of the arterioles and medial hypertrophy of the small arteries in 40% of 105 cases of mitral stenosis coming to autopsy There would seem no reason to suppose that active vaso constriction need be invoked if it were not for the fact that some cases of mitral stenosis submitted to mitral valvotomy show a prompt and striking fall of pulmonary arteriolar resistance Thus Dexter (1952) reports that two of twelve patients showed a pulmonary arteriolar resistance only one third of its preoperative value and two others showed a significant reduction Werko *et al* (1953) however did not note any striking changes of p a r after operation

Haddy *et al* (1953) induced mitral stenosis experimentally in dogs which allowed to survive developed an increase in pulmonary capillary pressure and pulmonary œdema the incidence of which was related to the height of the pulmonary capillary pressure Pulmonary arteriolar vascular resistance did not increase however which they suggested was due to the inadequate length of time allowed for the development of chronic organic changes in the vessel walls causing alteration of their elastic and/or viscous properties They obtained therefore no evidence of active pulmonary arteriolar vasoconstriction despite the rise of pulmonary capillary pressure and left atrial pressure Kopelman & Lee (1951) compared the intrathoracic blood volume in patients with mitral stenosis some of whom were in congestive failure with that in patients with left ventricular failure They found only a slight increase over the normal in the mitral cases but a considerable increase in those with left ventricular failure Since in both groups the cardiac output was similarly reduced they ascribed the differences to the more chronic nature of the obstructing process in mitral disease which caused anatomical changes in the pulmonary vessels compared with the relatively episodic and acute incidents of pulmonary congestion in left ventricular failure They did not commit themselves to claiming active pulmonary vasoconstriction in the mitral cases Similar findings with respect to the normality of intrathoracic blood volume in mitral stenosis were reported by Borden *et al* (1950) who also related this together with the absence of pulmonary congestion and œdema despite the pulmonary hypertension to a change of vascular resistance which was in their opinion caused by organic changes in the vessels Halmagyi *et al* (1953) have claimed that neurogenic pulmonary vasoconstriction is responsible for at least part of the pulmonary hypertension of mitral stenosis They made no measurements of left atrial or pulmonary capillary pressure merely calculating pulmonary vascular resistance from the formula $R = \frac{P_A \times 1332 \times 60}{CI}$ where CI is the cardiac index in ml /min It is dangerous to make pronouncements on changes of pulmonary vascular resistance when no measurements are made at any point downstream from the pulmonary artery itself However they found that sodium nitrite increased the cardiac index and lowered the pulmonary arterial pressure as did dibenamine and TEAB They then assumed that receptor bodies in the pulmonary vessels are sensitive to an elevation of pulmonary venous pressure and supposed that as a result reflex sympathetic vasoconstriction occurred in the arterioles of the pulmonary vascular tree It is the reviewer s opinion that they have in no way proved this point Fowler *et al* (1950) did show however that in four cases out of six with pulmonary hypertension the injection of tetraethyl ammonium chloride did cause a

significant lowering of the pulmonary arteriolar resistance whereas the drug had no effect on pulmonary arteriolar resistance in patients with normal pulmonary artery pressure They suggested that at least one component of the raised arteriolar resistance could be ascribed to autonomic vasoconstriction von Euler & Liljestrand (1946) studying anæsthetized cats breathing 10–11% O in N found that the resulting rise in pulmonary artery pressure was unaffected by stellatectomy and vagotomy and concluded that the pulmonary hypertension of anoxia was mediated through a local effect on the pulmonary arterioles Dirken & Heemstra (1948*a* *b*) and Rahn *et al* (1953) reported marked pulmonary vasoconstriction in a lung singly exposed to anoxia whilst the other lung ventilated with oxygen was unaffected This effect was not mediated by autonomic nerves Motley *et al* (1947) demonstrated that anoxia caused a marked rise in the pulmonary artery pressure accompanied by a slight fall in the cardiac output in five anæsthetized human subjects This also suggests that anoxic vasoconstriction occurred in the smaller lung vessels Westcott *et al* (1951) found that the inhalation of 100% O caused a definite reduction in the pulmonary arterial pressure of five patients with pulmonary hypertension As anoxia may cause constriction of the pulmonary vessels by a direct action on the smooth muscle of the arterioles it may be premature to postulate that there is increased neurogenic pulmonary vasoconstriction in conditions of chronic pulmonary hypertension As Westcott *et al* (1950) have pointed out the additional element of pulmonary arteriolar constriction which supervenes in mitral stenosis when the pulmonary capillary pressure exceeds 20–25 mm Hg may be the result of anoxia It seems reasonable to assume that such capillary pressures may be associated with the onset of œdema formation and consequent impairment of the delivery of oxygen On the other hand there seems no clear reason why autonomic blocking agents should lower the pulmonary arteriolar resistance in these patients unless some degree of autonomic vasoconstriction is present

Wood (1956) has stated that 30% of cases with critical mitral stenosis show vasoconstrictive pulmonary hypertension He injected acetylcholine (1 5 mg) directly into the pulmonary artery and found that the pulmonary arterial pressure and resistance fell immediately while the left atrial pressure and cardiac output rose He concluded that the high pulmonary resistance was protective in these patients

The question arises whether there are chemoreceptors in the lung vessels which responding to anoxia may initiate vasoconstriction Heymans & Heymans (1927) and Comroe (1939) denied the presence of such receptors and although Pi Suñer (1947) has claimed that they exist the bulk of evidence is against his views

Reflexes from the Left Heart

Perfusion Studies

Daly & Verney (1926) were the first to provide evidence that pressoreceptors existed in the left heart In an innervated heart lung preparation in which the aortic pressure was kept constant an increased pressure in the left side of the heart caused cardiac slowing The procedure employed (which entailed the retrograde passage of a cannula whose tip lay within a few millimetres of the coronary orifice) must have caused a simultaneous increase in pressure in both the coronary vessels and the left ventricle Aviado Li Calesnic & Bell (1951) and Aviado *et al* (1951) found that a rise of pressure in the

cooling the cervical vagi to 9–11°C (Dawes *et al* 1952 Dawes, 1952 1953) which suggested that the afferent fibres concerned were of reasonably large diameter—A fibres This conclusion was at variance with that of Jarisch & Zotterman (1948) who demonstrated that veratrine injection evoked an outburst of small slowly conducted potentials in cardiac afferent fibres whose nerve endings were believed to be situated in the ventricles

The afferent pathway of fibres which carry impulses responsible for the Bezold reflex is apparently complex Jarisch & Richter (1939*b* *c*) concluded that the afferents on the

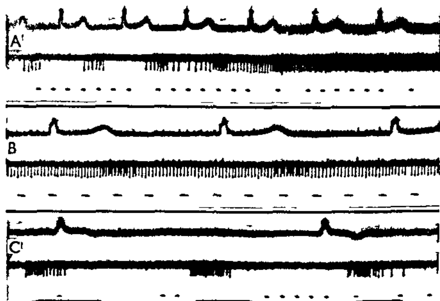


FIG 87 Impulses from two left atrial type B receptors following injection of 22μ veratridine into the right atrium 6 8 seconds before beginning of record A B recorded 5 6 seconds after A note that the fibre with the smaller spike is unaffected C shows the response of the receptor stimulated by veratridine to touching a part of the left atrium after cutting away the ventricles —(A S Paintal (1955*b*) *Quart J exp Physiol* 40 348)

right side ran from the ventricles behind the aortic arch to enter the right vagus as it crossed the right subclavian artery Jones (1953) found the fibres much more widely distributed as section of the upper cardiac branches of the right vagus did not abolish the reflex even after section of the left vagus The inferior cardiac vagal nerves entering the vagus trunk above and below the level of the junction of the v azygos with the superior vena cava were shown to contain Bezold afferent fibres These studies were made on cats In dogs Dawes and Widdicombe (1953) examined the distribution of Bezold afferents on the left side They concluded that most of these ran from the posterior surface of the left heart behind the left pulmonary artery to join the left recurrent laryngeal nerve as it crossed the aortic arch

Paintal (1955*b*) after a patient search has recently shown that veratrine and related substances activate ventricular receptors and some of both types (A and B) of the left atrial receptors The accompanying figures (Figs 86 and 87) from his paper provide convincing evidence of the probable role of these receptors in the Bezold effect Paintal has pointed

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vascularly isolated left heart caused reflex bradycardia and vasodilatation of the leg vessels A rise of pressure in the left atrium alone was ineffective Hence the receptors responsible must have lain in the ventricle The response was abolished by vagotomy No information exists as to whether these receptors cause any effects on breathing owing to the technical difficulty of closing the chest around the numerous perfusion tubes required As Aviado & Schmidt (1955) point out it is not surprising that the quantitative responses evoked by these methods are poor when one considers the technical difficulties entailed Gruhzit (cited by Aviado & Schmidt 1955) claims that the cardiac baroreceptors in the left ventricle of the cat appear to be about as sensitive as those in the sino aortic areas on the basis of results obtained with the technique of cardiac catheterization and circulatory blockade

Reflex Response to Veratrine—the Bezold Jarisch Reflex

The idea of cardiac pressoreceptors is an old one and dates from the work of Cyon & Ludwig (1866) These workers believed that the depressor (aortic) nerve arose from cardiac vagal receptors They suggested that these receptors reflexly controlled heart rate and stroke volume About the same time Bezold & Hirt (1868) first demonstrated the profound bradycardia hypotension and apnœa produced by the intravenous injection of veratrine They considered that the drug stimulated cardiac receptors and thereby induced reflex cardiovascular and respiratory effects Partly because they published their work in a little known journal and partly because Cyon and Ludwig s belief in the cardiac origin of the depressor nerve was shown to be false interest swung away from the investigation of cardiac vagal receptors and their influence on the circulation It was not until Jarisch (1938 1940 1941 1949) and his colleagues (Jarisch & Richter 1939*a* *b* *c*) revived the concept of proprioceptive receptors in the heart responsive to changes in intraventricular pressure some seventy years later that much further work was done on this topic Meanwhile the actions of the drug veratrine were sporadically investigated Pilcher & Sollmann (1915) claimed that veratrine stimulated the medullary vagal centre directly but Cramer (1915) stated that the effects produced were reflexly initiated however by the stimulation of vagal receptors in the lungs Cramer was at least partly right and was moreover the first to realize that systemic hypotension produced by the drug was independent of the bradycardia being due to reflex peripheral vasodilatation McNider (1925) confirmed Cramer s findings and showed that veratrine caused hypotension even after atropine he therefore stressed that the drug must cause reflex changes in arteriolar peripheral resistance Richter & Thoma (1939) disproved the claims of Pilcher and Sollmann by showing that veratrine injected into the vertebral arteries did not evoke bradycardia unless as was rarely the case it was re circulated to the heart in a sufficient concentration to stimulate the cardiac receptors Jarisch found that unilateral pneumonectomy with contralateral pulmonary vagotomy did not prevent the cardiovascular reflexes evoked by veratrine and hence concluded that the receptors concerned lay in the heart itself He proposed that these receptors might be ventricular normally responsive to stretch of the ventricular wall

Krayer Wood & Montes (1943) showed that the introduction of small doses of veratridine into an innervated heart lung circuit (connected to the head of the animal solely by the vago sympathetic nerves) caused bradycardia Vagotomy abolished the

response In the innervated heart lung head preparation veratridine also caused reflex vasodilatation of the vessels of the head as was revealed by a small fall in the perfusion pressure Moe Bassett & Krayer (1944) obtained bradycardia and hypotension which were maximal in 30 seconds after injection of 30–100 μg of veratridine into the right atrium Simultaneous measurements of left and right femoral blood flow indicated that a considerable reflex vasodilatation occurred Intra arterial injection of veratridine even

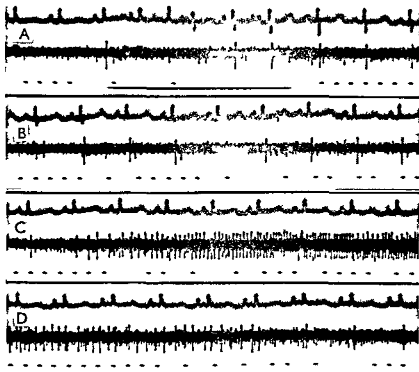


Fig 86 Response in a right ventricular fibre (large spike) following injection of 22 μg veratridine into the right atrium at signal in A Records of A B and C are continuous Injection response time is 5 6 second D was recorded 5 seconds after C From above downwards E C G im pulses in a fibre time in 1/10 second and injection signal A —(A S Paintal (1955*b*) *Quart J Physiol* 40 348)

in doses sufficient to produce a blood concentration of 1 in 3 000 caused no vasodilatation Atropinization which prevented reflex bradycardia after right atrial injection of veratridine did not abolish the changes of blood flow

Dawes (1947) has provided the most impressive indirect evidence for the belief that veratrine and its derivatives excite ventricular receptors The injection of these drugs directly into the coronary artery evoked the Bezold effect even with doses as small as 1/10 1/20th of the minimal effective intravenous dose Reflex effects were obtained when the drug was injected into the anterior descending branch of the left coronary artery which supplies only the left ventricle Hence wherever else the receptors might be some were undoubtedly in the left ventricle The Bezold effect thus evoked was blocked by

cooling the cervical vagi to 9–11°C (Dawes *et al* 1952 Dawes, 1952 1953) which suggested that the afferent fibres concerned were of reasonably large diameter—A fibres This conclusion was at variance with that of Jarisch & Zotterman (1948) who demonstrated that veratrine injection evoked an outburst of small slowly conducted potentials in cardiac afferent fibres whose nerve endings were believed to be situated in the ventricles

The afferent pathway of fibres which carry impulses responsible for the Bezold reflex is apparently complex Jarisch & Richter (1939*b* *c*) concluded that the afferents on the

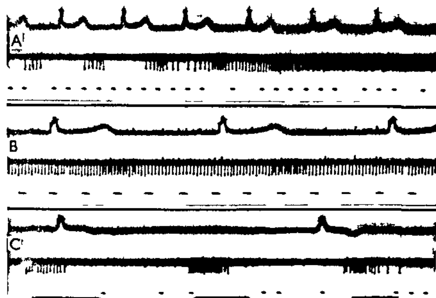


FIG 87 Impulses from two left atrial type B receptors following injection of 22μ veratridine into the right atrium 6 8 seconds before beginning of record A B recorded 5 6 seconds after A note that the fibre with the smaller spike is unaffected C shows the response of the receptor stimulated by veratridine to touching a part of the left atrium after cutting away the ventricles —(A S Paintal (1955*b*) *Quart J exp Physiol* 40 348)

right side ran from the ventricles behind the aortic arch to enter the right vagus as it crossed the right subclavian artery Jones (1953) found the fibres much more widely distributed as section of the upper cardiac branches of the right vagus did not abolish the reflex even after section of the left vagus The inferior cardiac vagal nerves entering the vagus trunk above and below the level of the junction of the v azygos with the superior vena cava were shown to contain Bezold afferent fibres These studies were made on cats In dogs Dawes and Widdicombe (1953) examined the distribution of Bezold afferents on the left side They concluded that most of these ran from the posterior surface of the left heart behind the left pulmonary artery to join the left recurrent laryngeal nerve as it crossed the aortic arch

Paintal (1955*b*) after a patient search has recently shown that veratrine and related substances activate ventricular receptors and some of both types (A and B) of the left atrial receptors The accompanying figures (Figs 86 and 87) from his paper provide convincing evidence of the probable role of these receptors in the Bezold effect Paintal has pointed

out that the long injection response times especially in the case of the left atrial receptors suggest that the veriloid alkaloids do not stimulate the cardiac receptors directly It is possible he says that the alkaloids may cause some environmental change perhaps ionic which constitutes the mechanism of stimulation

It would seem therefore that Jarisch s conception of proprioceptors in the heart wall is correct Many questions remain among which the first must be whether these receptors are exerting a tonic influence on the medullary centres It seems unlikely that the obvious phasic activity which can be recorded from their afferent fibres should be quite ineffective in modifying the behaviour of the cardio inhibitory and vasomotor neurones If this is so then we must admit that a proportion of the reflex vagal tone is due to these receptors as well as to those in the sino aortic areas Some evidence that this is the case is offered by the results seen in postural hypotension where reflex tachycardia and peripheral vaso constriction occur as reflex responses (Gilmore *et al* 1952) As Aviado & Schmidt (1955) have said the reflex vasoconstriction can be explained by the fall in aortic pressure but the earlier onset of tachycardia must arise from another source and this is likely to be represented by the cardiac receptors The immediate fall in right atrial pressure (which may be accompanied by a similar fall in the remainder of the cardio pulmonary circuit) would appear to offer an explanation of the tachycardia—a reduction of cardiac presso receptor activity causing a decrease in vagal tone Such a conception is very different from that which attributes the Bainbridge reflex acceleration to an increase in the impulse activity of atrial receptors This latter belief however is difficult to maintain in view of the results of Aviado *et al* (1951) Moreover the Bainbridge effect is often cited as the cause of cardiac acceleration in exercise it has been argued that the rise of atrial pressure caused by the increase in venous return excites atrial and possibly ventricular receptors which cause reflex tachycardia Landis Brown Fauteux & Wise (1946) showed that there is no increase in the mean atrial pressure in exercise This however does not mean that there is not an increase in the phasic excursions of the atrial pressure and it is this which is of most importance in exciting the mechanoreceptors of the atrium It is possible indeed that such an increase in atrial receptor activity may provide a useful reflex brake to the heart in conditions of exercise beating quickly under the triple influence of sympathetic stimulation chemical stimulation and raised temperature thereby tending to reduce the likelihood of extrasystoles

Volume Receptors—The Role of the Left Atrial Receptors in Maintaining Constant Blood Volume

Recent work has shown that the left atrial vagal receptors may form the sensory endings of a reflex which controls blood volume (Gauer *et al* 1954 1956 Henry *et al* 1956*a b* Henry & Pearce 1956 Pearce & Henry 1955) These authors showed first that negative pressure artificial respiration caused diuresis This was related by them to the congestion of the thoracic blood vessels produced by this type of ventilation As the effect was abolished by vagotomy they concluded that cardiac or pulmonary vascular receptors of vagal origin responsive to changes in pressure or to changes in distension of the vessel walls were affected in the circumstances of negative pressure ventilation Further work substantiated these conclusions Dogs were submitted to three forms of graded obstruction of their pulmonary circulation —

1 By the intravenous infusion of an aqueous suspension of glass beads (diameter 40–80 μ) sufficient to raise the mean pulmonary arterial pressure from 16 cm H_2O to *approximately 30 cm* H_2O.
2 By obstructing the pulmonary veins by means of steel snares. This required bilateral thoracotomy. After snaring the veins of both lungs the chest was closed and the pneumothorax was reduced. By adjusting the snares the mean pulmonary arterial pressure could be raised to 40 cm H_2O or more.
3 By introducing a rubber balloon into the left atrium. This was connected by polythene tubing to a water filled syringe. The chest was closed around the polythene tubing and the pneumothorax was reduced. The balloon was distended by the gradual injection of water until the pulmonary arterial pressure was increased by 15 or 20 cm H_2O.

Balloon distension or snare obstruction was maintained for 20 to 30 minutes. No tests were made for 2–4 hours following the completion of the operative procedure. They claim that this delay gave time for a decrease in the level of antidiuretic hormone secretion which Eisen & Lewis (1954) reported to be greatly increased for several hours following an operation.

Following injection of the beads there was no increase in urine flow, despite the increase in pulmonary arterial pressure. In the snare experiments there was no increase in urine flow although the rise of pressure occurred throughout the pulmonary vascular bed. However, in 37 balloon experiments in 13 dogs diuresis occurred on distension of the balloon despite the accompanying obstruction to the circulation (cardiac output being reduced from about 3¼ litres/min. to 2¼ litres/min. (these figures seem rather high). In 14 experiments the urine flow increased two to five fold. The results indicate that the left atrium is the most important reflexogenic region concerned. There was little change in right atrial pressure in these balloon experiments but as the authors point out there is no reason to exclude right atrial receptors from consideration in the initiation of such reflexes in the intact circulation. Farber, Becker & Eichna (1953) were unable to obtain a diuresis by distending the inferior or superior vena cava, but Henry *et al* (1956) say that the receptor network of these veins is limited to the mouths of the cavæ. Henry & Pearce (1956) later showed that balloon distension of the left atrium did in fact stimulate the atrial receptors as indeed might be expected. Similarly, negative pressure breathing or blood transfusion increased the impulse activity of the left atrial receptors, whereas pulmonary hypertension caused by snares on the pulmonary veins did not. The impulses in the left atrial receptors were blocked by cooling the vagus to 8°C. The diuretic response to balloon distension was also abolished by vagal cooling to 8°C.

Henry *et al* (1956) conclude that these sensory areas in the low pressure part of the cardiovascular system are responsible for the reflex control of blood volume. In hydræmic plethora, diuresis would thus alleviate the circulatory engorgement, and following hæmorrhage perhaps the reduction of tonic impulse activity from the atrial receptors would help to maintain the blood volume by reducing the water loss in the urine.

This excellent contribution to our knowledge is sufficient in itself. However, the authors proceed to label other circulatory responses as being due to reflexes initiated from the left atrial or volume sensitive receptors without having any evidence for their statements. They consider that the contraction of the spleen and peripheral veins and the

release of vasoconstrictor substances which occur following hæmorrhage insufficient to change the systemic arterial pressure are reflexly brought about by changes of activity of the atrial receptors There is an equally good reason to suppose that these circulation reactions are initiated from the sino aortic zones even though the mean systemic pressure is the same as before bleeding Ead Green & Neil (1952) have reported that the pulse pressure and the rate of rise of the pulse pressure are of considerable importance in determining the reflexogenic activity of the sino aortic baroreceptors There is no doubt that there is a reduced pulse pressure after hæmorrhage which has been insufficient to lower the mean systemic pressure particularly as the heart rate increases in these circumstances

It is interesting to note that balloon distension of the left atrium did not cause any change in the pulse rate or the respiratory rate in the experiment shown in Figure 3 of the paper of Henry *et al* (1956) This is despite the marked rise which occurred both in the pulmonary arterial pressure and the left arterial pressure Moreover there were only trivial changes in the systemic blood pressure during balloon distension although they avow that a marked reduction of cardiac output occurred Presumably compensatory systemic vasoconstriction took place and this can hardly be attributed to the results of stimulation of the left atrial receptors for the compensatory responses were the opposite of those which they ascribe to their reflexogenic zone Probably the sino aortic regions were the source of these compensatory reflexes

Pearce Henry & Chapman (1956) who again refer to the role of the atrial receptors in providing information from the low pressure system to the higher centres responsible for cardiovascular and body fluid homeostasis advance fresh evidence of the effects of hæmorrhage on the atrial receptors type B After severe bleeding or during increased intrathoracic pressure the timing of the discharge shifts from the normal diastolic burst to a systolic discharge They attribute this to a change in the distensibility of the atrial wall They propose that a predominantly systolic discharge pattern may signify a state of high tone and low filling to the central control mechanisms whereas a pre dominantly diastolic timing might do the opposite They consider that such a shift in timing of the discharge may play a role in triggering vasovagal syncope They also hazard the opinion that chronic distension of the atrium such as may occur in mitral stenosis might cause disturbed activity of the atrial receptors

Chapter 24

CARDIOVASCULAR REFLEXES OF UNCERTAIN ORIGIN

The preceding account of the cardiopulmonary reflexes makes no mention of the universally known Bainbridge reflex described by Bainbridge in 1915 This does not mean that we do not believe in its existence although there are those who hold this view (Jarisch & Zotterman 1948 Wiggers 1949) On the contrary we are firmly of the opinion not only that it exists but that it is important in conditions of increased circulatory activity It is somewhat curious to consider that the Bainbridge effect is the one reflex from the heart itself which is known by every medical student Our order of presentation of the cardiopulmonary reflexes has been conditioned rather by the positive evidence which exists for the anatomical site and physiological characteristics of the receptors which form the sensory endings of them To date there is no evidence that any of the receptors so far described can initiate cardio-acceleratory reflexes Hence we present the evidence for and against the Bainbridge effect separately In addition we draw attention to two other phenomena in which reflexes from the chest are implicated although the receptors responsible are not known These are the reflex vasoconstriction of the peripheral vessels which is produced on taking a deep inspiration and the phenomenon of sinus arrhythmia which although it can undoubtedly be related to a central origin of irradiation from the discharging inspiratory centre may also have an additional reflex origin from the cardio pulmonary area in the intact circulation

The Bainbridge Reflex

In 1915 Bainbridge showed that the intravenous injection of blood or saline produced tachycardia in dogs anæsthetized by morphine and ether Section of the rami accelerantes reduced but did not abolish this response Atropinization though markedly reducing the tachycardia produced by intravenous infusion in an intact animal did not abolish it Only bilateral vagotomy was completely effective in preventing the response Bainbridge concluded that the tachycardia was elicited reflexly by stimulation of vagal receptors on the venous side of the heart He pointed out that the intravenous infusion caused a rise of venous pressure sufficient to raise the diastolic pressure and to dilate the heart and left unanswered the question of whether the effective stimulus of the receptors was a rise of venous and diastolic pressure or whether it was an increased tension in the ventricular muscle fibres He suggested that the afferent impulses caused a reflex reduction in vagal inhibitory impulse activity with a simultaneous increase in cardiosympathetic impulse traffic

Sassa & Miyazaki (1920) elicited tachycardia by inflating balloons introduced into the right atrium of anæsthetized dogs The effect was abolished by vagotomy There seems however no reason to attribute the reflex tachycardia to the rise in right atrial pressure as they did for inflation of the balloon would seriously affect venous return de Graff &

Sands (1925) could only obtain tachycardia after intravenous infusion in about half of their series of dogs indeed vagotomy did not always abolish the response to infusion obtained in the intact animals

Anrep & Segall (1926) on increasing the venous return in an innervated heart lung preparation induced tachycardia Atropinization reduced and vagotomy abolished the response Tachycardia could still be produced after section of the pulmonary vagal branches and removal of the parietal pericardium In several instances tachycardia was observed where no rise of mean right atrial pressure attended the increase of venous return They were not convinced that the receptors responsible for the reflex lay only on the venous side of the heart Their results are important in showing that the reflex tachycardia of infusion can at least be produced by afferent effects elicitable solely from the cardio pulmonary area Tiitso (1937) evoked tachycardia in the isolated perfused mammalian heart by raising the perfusion pressure and concluded that the effect was a direct one due to stimulation of the sino atrial node by increased intracardiac tension It is of some interest to remark here that Knowlton & Starling (1912) reported that alteration of endo cardiac pressure or rate of venous inflow had no effect whatever on the rate of beat of the denervated heart lung preparation On the other hand it has long been known that an increase of tension in the ventricular fibres of the frog heart causes acceleration of the beat and renders the heart very irresponsive to efferent vagal stimulation (Ludwig & Luch singer 1881 Sewall & Donaldson 1882) A recent paper by Blinks (1956) supports Tiitso s claims Tiitso made an important contribution by showing that the cardio acceleratory response of infusion in the intact animal was abolished by right vagal section only because the heart rate was increased almost to maximum by the vagal section itself Thus if the peripheral end of the right vagus were stimulated so as to slow the heart rate to a more normal value infusion again elicited tachycardia even though both vagi had been cut Ballin & Katz (1941) reinvestigated the Bainbridge effect very carefully In sixteen experiments on twelve dogs of which all but two were unanæsthetized they injected 150–200 ml of mammalian Ringer solution The infusion was completed in periods which ranged from 7 to 96 seconds The unanæsthetized dogs with one exception showed cardiac acceleration (range—14 to 78 beats per minute) the peak of which occurred some 30 seconds after the start of the infusion The tachycardia lasted some minutes In experiments in which the rate of infusion was rapid the arterial pressure rose during in fusion and often transient bradycardia supervened early in the injection period This was considered to be of sino aortic origin In such experiments the venous pressure rose to over 40 cm H O during infusion and remained high for several minutes Such a rise of venous pressure was justifiably considered by the authors to indicate an engorgement of the pulmonary circuit in addition to that of the right heart In some dogs the right atrium was by passed by a tube which led from the venæ cavæ directly to the cavity of the right ventricle Rapid infusion still elicited tachycardia in these dogs Conversely distension of the superior atrio caval orifice by a rubber balloon did not evoke tachycardia In these last experiments venous return was not obstructed by the balloon From their results Ballin & Katz inferred that the Bainbridge reflex was initiated by the stimulation of receptors other than those situated in the right atrium

Bouckaert & Pannier (1942) increased the venous return to the heart of a recipient dog by connecting the carotid artery of a donor dog to the jugular vein of the recipient The

recipient dog s carotid artery was in turn anastomosed with a jugular vein of the donor They obtained cardiac acceleration in the recipient on each occasion that the a v anastomoses were opened

Jarisch & Zotterman (1948) reported that intravenous infusion never evoked tachy cardia in the cat Wiggers (1949) states that the intravenous injection of blood or saline does not cause cardiac acceleration in the dog Aviado *et al* (1951) infused 200 ml of heparinized blood by means of a Dale Schuster pump via a metal cannula whose tip ended in the right atrium The infusion when made rapidly (5 seconds) frequently caused bradycardia and hypotension when made for the first time Subsequent infusions gave less clear cut results even though precautions were taken against unduly altering the blood volume during the course of long experiments Perfusion of the isolated right side of the heart was carried out by pumping blood from the superior and inferior venæ cavæ into the right atrium whence it passed through the right ventricle and was collected through a cannula in the pulmonary artery In such experiments the characteristic effect of an elevated pressure in the right side of the heart was bradycardia and hypotension The response was abolished by atropinization The receptors responsible were considered to lie both in the right atrium and in the pulmonary bifurcation as the effect could be evoked by raising the pressure in either locality The heart rates of these preparations were all rather high although the authors make no comment on this Aviado *et al* found that *tachycardia might occur in these preparations when the perfusion pressure of the right* heart was increased if the tests were made late in the course of the experiment

Coleridge & Linden (1955) showed that the efficacy of rapid intravenous infusion in eliciting tachycardia was essentially related to the initial heart rate of the dog If the control rate was unduly rapid then infusion never evoked any convincing cardio acceleration indeed bradycardia often resulted in these circumstances Coleridge & Linden have stressed that all the evidence in favour of a Bainbridge effect suggests that it is due to a release of vagal restraint Hence an intravenous infusion can hardly be ex pected to produce the effect in an animal whose control heart rate shows little sign of any initial vagal tone The same authors in a later paper have published the results of opening arterio venous fistulæ on the heart rate of the anæsthetized dog They found cardiac acceleration was so produced providing that the control heart rate was not unduly high (not more than 120–170 in most cases) For a given fistula flow the extent of the increase in heart rate appeared to be related inversely to the initial heart rate They regard the opening of an arterio venous fistula as the most convenient method of regulating the venous return in experimental studies of the Bainbridge reflex They found that opening the fistula produced very variable changes in mean right atrial pressure Simultaneous measurements of heart rate and mean right atrial pressure showed no obvious relationship However they point out that a true measure of the distending force within the atrium will be obtained only by recording effective atrial pressure They consider that changes in the rhythm and in the form of the atrial pressure curve (dynamic atrial pressure) apart from alterations in the height of the mean pressure may play an important part in determining the stream of vagal afferent impulses generated by a rise in atrial pressure The figure given in their paper shows that the opening of an arterio venous fistula caused a marked increase in right atrial systolic pressure although the mean atrial pressure remained unaltered They consider that further measurements should be made of the changes in

dynamic effective atrial pressure in order to investigate the possibility of a relationship between atrial pressure and the adequate stimulus for the Bainbridge reflex

It is difficult to ignore the positive results of Anrep & Segall Ballin & Katz and Coleridge & Linden In considering the cardiovascular effects of an increased venous return we must admit that an increase in cardiac output is likely to be prominent Hence the arterial pressure will rise and as a result an increase in baroreceptor activity of the sino aortic nerves must occur which will both lower arteriolar peripheral resistance and increase cardiac vagal tone Any cardiac acceleration which follows an increase in venous return must occur despite such opposition Moreover there is now considerable evidence for the presence of various cardio pulmonary receptors which when stimulated cause reflex bradycardia Such receptors include —

(1) Right atrial receptors—(A & B) Aviado & Schmidt have claimed that a rise in right atrial pressure produces bradycardia Ballin & Katz merely stated that distension of the atrio caval junction did not cause tachycardia
(2) Pulmonary arterial receptors situated in the pulmonary conus of bifurcation Aviado & Schmidt (1955) claim that a rise in pulmonary arterial pressure stimulates vagal receptors in this region and causes bradycardia
(3) Pulmonary deflation receptors (Paintal 1955*a*) sensitized or even stimulated by congestion of the lung such as is likely to occur following a rapid increase in venous return Stimulation of these receptors leads to reflex bradycardia (as part of the pulmonary depressor chemoreflex)
(4) Left atrial and left ventricular receptors whose excitation causes bradycardia (coronary chemoreflex receptors) Paintal has shown (1955*b*) that an increase in pressure in the left side of the heart increases their activity Thus a formidable array of opposing reflexes must be overcome before any reflex cardiac acceleration can be expected to occur on increasing venous return The Bainbridge reflex receptors are quite unknown They are unlikely to be situated in the right atrium or the atrio caval junction although Nonidez (1937) in describing vagal receptors in this vicinity referred to them as the afferent receptors of the Bainbridge reflex Ballin & Katz however clearly stated that the Bainbridge effect could be evoked even when the right atrium was by passed This is of more value as positive evidence than that afforded by distending balloons umbrellas and other unnatural temporary tenants of the right atrium Apart from such devices causing an entirely abnormal type of atrial stimulation there is no guarantee that they do not cause distortion of neighbouring structures such as the pulmonary veins coronary sinus etc

Aviado & Schmidt (1955) believe that the Bainbridge effect when it does occur arises as a result of stimulation of chemoreceptors supplied by the vago depressor trunk which might well be activated by the changes in gas content acidity tonic balance and viscosity of the blood associated with the massive intravenous infusion This is unlikely for a variety of reasons Foremost among these is the evidence that chemoreceptor stimulation does not cause tachycardia (Neil 1956) Moreover even if it did the author has yet to see chemoreceptor stimulation as a result of infusions of saline Ringer Locke or gum acacia solutions

Ph Knoll (1881) is credited by H E Hering with the discovery that the stimulation of afferent fibres in the cervical vagus causes marked tachycardia Hering (1924*a*) himself

confirmed and extended these results and demonstrated that electrical stimulation of the cervical vagus using faradic currents which were barely detectable to the tongue induced *a tachycardia which was not increased by section of both vagi* Anrep Pascual & Rossler (1936) likewise confirmed these findings and claimed that the reflex tachycardia was induced by feeble faradic stimulation of the central end of the pulmonary vagal fibres Further investigation of these effects is required It is particularly interesting that only very feeble stimulation will induce reflex acceleration stronger stimulation evokes the more common response of cardiac slowing This suggests that the afferent fibres concerned are of the large myelinated type

de Waele & Van de Velde (1940) have claimed that the right atrium is the site of receptors whose excitation causes vasoconstriction and hypertension The afferent pathway of this reflex was stated as being via the intercostal nerve roots of the first three thoracic segments The receptors were claimed to be activated by a reduction in the venous return Their claims have not been confirmed

Vasoconstriction in the Finger after Deep Inspiration

Goetz (1935) observed that the volume of the finger decreased when a deep breath was taken and shortly afterwards Bolton Carmichael & Sturup (1936) confirmed this Wilkins Doupe & Newman (1938) noted a decrease in blood flow as did Herzmann & Dillon (1939) Mulinos & Shulman (1939) actually observed the capillary loops of the nail bed and observed a slowing of the flow through them when a deep breath was taken by the subject Bolton Carmichael & Sturup could not evoke the reflex vasoconstriction in subjects who made a deep abdominal inspiration and suggested that the afferent endings might be situated in the chest wall rather than the thoracic viscera None of these authors had considered whether the arterial blood pressure itself fell during a deep thoracic inspiration as Lewis (1908) had first shown and which has been confirmed by Battro Segura Elicabe & Araya (1944) Gilliatt (1948) therefore re examined the problem recording the finger volume optically by a glass plethysmograph and simultaneously recording the systolic blood pressure optically He showed that vasoconstriction occurred after a voluntary deep inspiration or after passive deep inflation of the chest with air under positive pressure Vasoconstriction did not occur after obstructed inspiratory or expiratory efforts nor after a forced expiration Respiratory fluctuations in systolic pressure which accompanied these phenomena bore no constant relationship to the finger vasoconstriction Gilliatt therefore concluded that the reflex was not initated by sino aortic reflexes He noted that abdominal breathing restricted the volume of air which could be *inspired and that vasoconstriction of the finger could be obtained only with fast rates of* inspiration Such constriction as was then obtained was comparable with that caused by thoracic inspiration of similar rate and depth

Gilliatt Guttmann & Whitteridge (1948) examined these reflex vasomotor responses in the fingers and toes of paraplegic patients Inspiratory vasoconstriction was still found in the fingers in patients with spinal transection above the level of the sympathetic outflow to the hands It was concluded that in such patients the constriction must have been a purely spinal reflex taking place in the thoracic region of the cord All observations were consistent with the view that the afferent fibres concerned in this reflex entered the spinal cord mainly in the upper thoracic segments

The receptors and afferent pathways of this reflex remain obscure However Holmes & Torrance (1955) recently found afferent fibres in the inferior cardio sympathetic nerve which arose from mediastinal receptors These were excited by considerable displacements of the chest and might serve as the receptors for this reflex

Sinus or Respiratory Arrhythmia

Ludwig in 1847 was the first to describe respiratory changes of the heart rate Einbrodt (1860) claimed that slowing of the heart was the response to inflation of the lungs by positive pressure E Hering (1871) however pointed out that Einbrodt used excessively high inflation pressures and showed that inflation at pressures not greater than 15 mm Hg caused cardiac acceleration whether the chest was closed or open Moreover Hering was able to evoke tachycardia by lowering the intrathoracic pressure Section of the vagi abolished the response Fredericq (1882) observed that cardiac arrhythmia persisted in animals with open chests in which no lung movement was occurring Snyder (1915) confirmed these observations Heymans & Heymans (1928) investigated the problem using the perfused head preparation A donor dog (A) perfused the head of a recipient (B) which was connected to its trunk only by the vagi Activity of the respiratory centre of (B) was sampled by recording the movements of the alæ nasi The trunk of (B) was artificially ventilated The femoral pulse of (B) was recorded The pulse showed an arrhythmia which was in time with the discharges of the respiratory centre as revealed by the alæ nasi movements The arrhythmia was quite independent of the rate of artificial ventilation (Heymans 1929*d*) This experiment has been widely quoted as evidence of the central origin of sinus arrhythmia Irradiation of activity from the medullary respiratory centre is supposed to affect the neighbouring cardiac centres Needless to say the experiment proves only that in these rather abnormal conditions sinus arrhythmia can be caused solely by such an irradiation It does not exclude the possibility of contributory reflexes from the lungs or cardio pulmonary areas playing a role in the intact animal H E Hering (1930) stated that inflation itself caused two reflex effects on the heart rate If the inflation were mild then cardiac acceleration was the rule but this gave place to cardiac slowing as the force and extent of inflation was increased Anrep Pascual & Rossler (1936) were able to confirm E Hering s observation that mild inflation caused cardiac acceleration They found it immaterial whether the chest was open or closed Positive and negative pressure ventilation were equally effective in evoking tachycardia during the phase of lung expansion The respiratory arrhythmia of the pulse was greatly affected by the state of vagus tone—if this were of medium intensity sinus arrhythmia was obvious If on the other hand vagal tone were almost absent then no arrhythmia could be seen These results are in agreement with those of *H E Hering (1930)* who noted disappearance of arrhythmia after section of both vagi and carotid occlusion Schweitzer (1935*b*) made some interesting observations on sinus arrhythmia finding that occlusion of the common carotid arteries which caused cardiac acceleration abolished the arrhythmia conversely a rise of sinus pressure which caused systemic hypotension and bradycardia was attended by very marked sinus arrhythmia (Fig 88) (See also Schweitzer 1937) Anrep and his colleagues (1936*b*) analysed further the contribution of the sensory mechanisms of the lungs They found that weak stimulation of the vagal afferents from

the lungs caused tachycardia due to loss of vagal tone while strong stimulation increased vagal tone They concluded that the lungs were a constant source of impulses which exerted an inhibitory influence upon the cardiac vagal centre This influence was maximal during inflation of the lungs and minimal but not entirely absent during their deflation In further experiments the same authors analysed the central mechanism of the respiratory arrhythmia of the pulse They excluded the complicating effects of lung afferents by cutting the vagi above the lung roots Using the innervated heart lung preparation in which the head is vascularly isolated and separately perfused they were able to increase

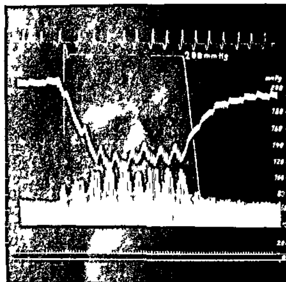


Fig 88 Dog Left common carotid artery ligated and left aortic nerve cut Right carotid sinus isolated by Moissejeff technique Records from above downwards respiration blood pressure heart rate (Fleisch)—note time Scale of heart rate recorded on the left A sudden rise of sinus pressure from 0–200 mm Hg causes reflex bradycardia and hypotension Note the development of conspicuous sinus arrhythmia —(A Schweitzer (1937) *Die Irradiation Autonomer Reflexe*)

the CO tension in the head so as to arouse obvious rhythmic activity of the respiratory centre as evinced by movements of the larynx The heart rate increased during each period of inspiratory discharge and slowed immediately after its cessation If the CO tension in the head circulation was lowered the central arrhythmia diminished *pari passu* with the respiratory centre activity The central arrhythmia was ascribed to a diminution of vagal tone during inspiration Anrep *et al* were unable to disprove that the sympathetic acceleration fibres played a role After section of the cervical vagi they hoped to ob ain a preparation in which arrhythmia might persist Invariably however the cardiac acceleration following vagal section was so marked that it was impossible to determine whether arrhythmia was present In this context it may be mentioned that the inferior cardiac sympathetic nerve (Bronk 1933–34) show volleys which are synchronous with inspiration (see also Fig 89) On the other hand the thoracic exposure required for the recording of such impulses is such as to make the conditions far removed from normal Anrep concluded his analysis by stating that the cardiac vagal centre stands under two inhibitory influences which act directly upon it one arises in the lungs and is especially strong during their inflation the other arises in the respiratory centre In addition to this the tone of the vagus centre is affected by the lungs in an indirect way through the Hering Breuer reflex Thus each inflation affects the vagus centre in two opposite ways On the

one hand by a direct reflex it induces an inhibition of the vagus centre and on the other hand simultaneously but indirectly it antagonizes this inhibition by cutting short the activity of the respiratory centre Conversely a deflation of the lungs diminishes the direct reflex inhibition of the vagus centre by cutting short the afferent impulses reaching it from the lungs but at the same time it indirectly antagonizes this effect by stimulating the activity of the respiratory centre (See also Anrep (1936))

Joels & Samueloff (1956) have recently provided an alternative demonstration of the contribution of central mechanisms to sinus arrhythmia Anæsthetized animals were

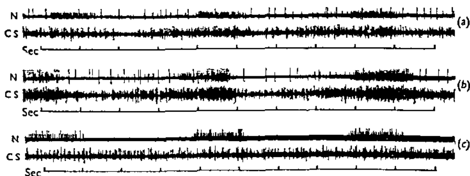


Fig 89 Respiratory and vasomotor centre activity during diffusion respiration in a cat as illustrated by the action potential discharges in the recurrent laryngeal and cervical sympathetic nerves In each strip records from above downwards recurrent laryngeal nerve (N) central end of cervical sympathetic nerve (C S) time in seconds (a) Control period there is a rhythmic discharge in the recurrent laryngeal nerve each burst of impulses being accompanied by an increase in the cervical sympathetic discharge (b) 1 minute after the beginning of diffusion respiration synchronization of the recurrent laryngeal and cervical sympathetic activity is still present Both discharges are intensified (c) After 16 minutes diffusion respiration the recurrent laryngeal discharge is diminished in intensity and the cervical sympathetic discharge no longer shows any rhythmicity —(N Joels and M Samueloff (1956) *J Physiol* **133** 360)

allowed to breathe oxygen for 30–45 minutes in order to secure denitrogenation Succinyl choline was then injected in order to paralyse the respiratory musculature Activity of the respiratory centre was sampled by recording the impulse activity in the motoneurones of the recurrent laryngeal nerve (Green & Neil 1955) Following the cessation of the respiratory movements the respiratory centre continued to discharge rhythmically for periods up to half an hour The animal survived for longer periods than this by diffusion respiration (Draper Whitehead & Spencer 1947) Simultaneous recordings of impulse activity of the cervical sympathetic nerves showed phasic activity in time with the inspiratory discharge of the laryngeal motoneurones (Fig 89) The heart rate showed accentuated sinus arrhythmia in time with the laryngeal motoneurone discharges As the impulse activity of the laryngeal neurones became feebler sinus arrhythmia disappeared and there was no longer any rhythmicity in the impulse activity in the sympathetic nerve

REFERENCES

ABE, K (1936) *Tohoku J exp Med* **29** 115
ABRAHAM A (1941) *Állatt Ko lem* **38** 179
ABRAHAM A (1942) *Acta Univ S eged Acta Zool* **1** 32
ABRAHAM A (1943) *Állatt Ko lem* **40** 242
ABRAHAM A (1945) *Ibid* **42** 14
ABRAHAM A (1949) *Z Zellforsch* **34** 208
ABRAHAM A (1949) *Hung acta biol* **1** 157
ABRAHAM A (1951) *Ann Biol Univ Hung* **1** 325
ABRAHAM A (1951) *Acta Univ S eged Acta Zool* **3** 13
ABRAHAM A (1953) *Acta biol acad Sci Hung* **4** 69 and 307
ABRAHAM A (1955) *Acta Univ S eged acta biol* **1** 125
ABREU B E RICHARDS A B ALEXANDER W M & WEAVER L C (1954) *J Pharmacol* **112** 73
ACKERMANN T (1872) *B rl Klin Wschr* 3
ADAIR E S CORDERO N & SHEN T C (1929) *J Physiol* **67** 288
ADAMS W E (1952) *Anat Rec* **113** 1
ADAMS W E (1953) *J Morph* **92** 115
ADAMS W E (1955) *Amer J Anat* **97** 1
ADAMS W E (1957) *J Anat Lond* **91** 207
ADDISON W H F (1941) *Biol Bull Wood s Hole* **81** 293
ADDISON W H F (1937) *Ibid* **77** 314
ADDISON W H F (1944) *Anat Rec* **88** 418
ADDISON W H F (1945) *Ibid* **91** 264
ADDISON W H F & COMROE J H (1937) *Anat Rec* **67** (Suppl 3) 2
ADDISON W H F & COMROE J H (1938) *Ibid* **70** (Suppl 3) 2
ADRIAN E D (1926) *J Physiol* **61** 49
ADRIAN E D BRONK D W & PHILLIPS G (1932) *Ibid* **74** 115
ADRIAN E D & ZOTTERMAN Y (1926) *Ibid* **61** 425
AGOSTONI E CHINNOCK J E DALY M DE B & MURRAY J G (1957) *Ibid* **135** 182
ALEXANDER R S (1945) *Amer J Physiol* **143** 698
ALEXANDER R S (1946) *J Neurophysiol* **9** 205
ALEXANDER R S (1954) *Circ Research* **2** 140
ALEXANDER R S (1954) *Ibid* **2** 405
ALEXANDER W A RICHARDS A B & ABREU B E (1953) *Fed Proc* **12** 297
ALPERT L K & THOMAS C B (1943) *Bull Johns Hopkins Hosp* **72** 274
ALVAREZ BUYULLA R (1953) *Abstr Comm XIX Internat Physiol Congress* 161
ALVERYD A & BRODY S (1948) *Acta physiol scand* **15** 140
AMANN A & JARISCH A (1943) *Arch exp Path Pharmak* **196** 275
AMANN A JARISCH A & RICHTER H (1941) *Ibid* **197** 590
AMANN A JARISCH A & RICHTER H (1941) *Ibid* **198** 158
AMANN A & SCHAEFER H (1943) *Pflug Arch g s Physiol* **246** 757
ANDERSCH E P (1797) Tractatio anatomico physiologica de nervis humani corporis aliquibus quam edidit Ernst Phillip Andersch Regimonti (cited by Mayer 1865)
ANDERSSON B KENNEY R A & NEIL E (1950) *Acta physiol scand* **20** 203
ANITCHKOV S V (1935) *Abstr Comm XV Internat Physiol Congress* 10
ANITCHKOV S V (1935) *Arch int Pharmacodyn* **51** 367
ANITCHKOV S V (1937) *Sechenov J Physiol* **21** 27
ANITCHKOV S V (1937) *Arch int Pharmacodyn* **60** 61
ANITCHKOV S V (1947) *Sechenov J Physiol* **33** 367
ANITCHKOV S V (1951) *Ibid* **37** 28
ANITCHKOV S V (1953) *Abstr Comm XIX Internat Physiol Congress* 170
ANITCHKOV S V (1955) *Pharmacology and Toxicology (Moscow)* **18** 3
ANITCHKOV S V ZAKUSSOV V V KUSNEZOR A J & POLIAKOV N G (1936) *Sechenov J Physiol* **21** 809
ANREP G V (1936) *Lane Medical Lectures* **3** 227
ANREP G V PASCUAL W & ROSSLER (1936) *Proc Roy Soc* **B** **119** 191 and 218

ANREP G V & SEGALL, H N (1926) *J Physiol* 16 215
ANREP G V & STARLING E H (1925) *Proc Roy Soc* B 97 463
ANUFRIEW W N (1928) *Z ges Anat I Z Anat Entw Gesch* 86 639
AOMURA T (1930) *Tohoku J exp Med* 15 1
ARA G (1934) *Arch Fisiol* 33, 332
ARAKI T Z (1891) *Hoppe Seyl Z* 15 335
AREY L B (1942) *Developmental Anatomy* Saunders London
ARGAUD R (1941) *Bull Histol Tech micr* 38 3
ARNOLD F (1851) *Handbuch der Anatomie d Menschen* Vol 2 2nd Section Freiburg
ARNOLD J (1865) *Virchows Arch* 33 190
ASK UPMARK E (1935) *Acta psychiat Kbh* Suppl 6
ASK UPMARK E (1954) *Acta med scand* 149 161
ASK UPMARK E & FAJERS G M (1956) *Acta med scand* 155 275
ASMUSSEN E & CHIODI H (1941) *Amer J Physiol* 132 426
ASMUSSEN E & NIELSEN M (1946) *Acta physiol scand* 12 171
ASMUSSEN E & NIELSEN M (1953) *Ann Rev Physiol* 15 85
ASRATIAN S (1938) *Sechenov J Physiol* 24 982
ASTEROTH H & KREUZIGER H (1951) *Z Kreisl Forsch* 40 11
ÅSTRAND P O (1954) *Acta physiol scand* 30 335
ÅSTRAND P O (1954) *Acta physiol scand* 30 343
ÅSTROM A (1952) *Acta physiol scand* 27 Suppl 98
ATANACKOVIC D (1950) *Arch int Pharmacodyn* 83 277
ATANACKOVIC D (1951) *Arch int Pharmacodyn* 85 78
ATANACKOVIC D & DAHLGAARD MIKKELSEN S (1950) *Arch int Pharmacodyn* 84 308
AUB J C (1920) *Amer J Physiol* 54 388
AUBERT H & ROEVER G (1868) *Pflug Arch ges Physiol* 1 211
AVIADO D M CERLETTI A ALANIS J BULLE P H & SCHMIDT C F (1952) *Amer J Physiol* 169 460
AVIADO D M LI T H CALESNIK B & BELL R (1951) *Fed Proc* 10 7
AVIADO D M LI T H KALOW W PESKIN E W TURNBULL G L & HESS M E (1951) *Amer J Physiol* 165 261
AVIADO D M PONTIUS R G & LI T H (1950) *J Pharmacol* 99 425
AVIADO D M PONTIUS R G & SCHMIDT C F (1949) *J Pharmacol* 97 420
AVIADO D M & SCHMIDT C F (1950) *Circulation* 6 666
AVIADO D M & SCHMIDT C F (1955) *Physiol Rev* 35 247
AXELROD D R & PITTS R F (1952) *J appl Physiol* 4 593

BABAK E (1909) *Pflug Arch ges Physiol* 127 481
BACQ Z M BREMER F BROUHA L & HEYMANS C (1939) *Arch int Pharmacodyn* 62 460
BACQ Z M BROUHA L & HEYMANS C (1934) *Arch int Pharmacodyn* 48 429
BAGOURY M M & SAMAAN A (1941) *J Egypt med Ass* 24 211
BAILEY P & BREMER F (1938) *J Neurophysiol* 1 405
BAINBRIDGE F A (1914) *J Physiol* 48 332
BAINBRIDGE F A (1915) *J Physiol* 50 65
BALLIN R I & KATZ L N (1941) *Amer J Physiol* 135 202
BANNISTER R G (1956) *Brit med Bull* 12 222
BANNISTER R G & CUNNINGHAM D J C (1954) *J Physiol* 125 118
BANUS M G CORMAN H H PERLO V P & POPKIN G L (1944) *Amer J Physiol* 142 121
BARANY E VON (1943) *Acta physiol scand* 5 431
BARCROFT J CAMIS M MATHISON C G ROBERTS F G & RYFFEL J H (1914) *Phil Trans Roy Soc B* 206 49
BARCROFT H BASNAYAKE V CELANDER O COBBOLD A F CUNNINGHAM D J C JUKES M G M & YOUNG M (1956) *Abstr XXth Internat Congr Physiol* 61
BARCROFT H EDHOLM O G MCMICHAEL J & SHARPEY SCHAFER E P (1944) *Lancet* i 489
BARER G R & NUSSER E (1953) *Brit J Pharmacol* 8 315
BARTELS H & WITZLEB E (1956) *Pflug Arch ges Physiol* 262 466
BATTRO A SEGURA R G ELICABE L A & ARAYA E (1944) *Arch intern Med* 73 29
BAYLISS W M (1893) *J Physiol* 14 303
BAYLISS W M (1908) *J Physiol* 37 264
BEARD E F BELL, A L L HOWELL, T W (1953) *J Aviation Med* 24 494

BECK A & LAUBER H J (1929) *Pflug Arch ges Physiol* **221** 499
BEKESY E (1889) *Zbl Physiol* 2 176
BELENKY M L (1949*a*) *Bull Biol Méd exp U R S S* 26 297
BELENKY M L (1949*b*) *Bull Biol Med exp U R S S* 28 64
BELENKY M L (1951) *C R Acad Sci U R S S* 76 305
BELOUS A A (1953) Quoted by Anitchkov (1955)
BEMMELEN J F VAN (1886) *Zool An* 9 528
BEMMELEN J F VAN (1887) *Zool An* 10 88
BENEKE R (1925) *Virchow s Arch* 254 722
BENOIT A (1928) *Arch Biol Paris* 38 219
BENSEN T (1880) *Berl Klin Wschr* 17 248
BERGAMI G & SACHI U (1935) *Arch Fisiol* 5 104
BERGER, E Y GALDSTON M HORWITZ S A (1948) *J clin Invest* 28 648
BERKLEY H J (1893) *J comp Neurol* 3 107
BERKLEY H J (1894) *Johns Hopkins Hosp Rep* 4 248
BERNARD C (1851) *C R Soc Biol Paris* p 163
BERNARD C (1952) *C R Soc Biol Paris* p 169
BERNARD C (1857) *Leçons sur les Effets des Substances Toxiques et Medicamenteuses* ed 2 p 348 Bailliere Paris
BERNARD C (1859) *Proprietés Physiologiques des Liquides de L orgasme* Tome II p 162 Baillière Paris
BERNHARDT E (1868) *Anatomische und physiologische Untersuchungen des Nervus depressor* Inaug Diss Dorpat
BERNSTEIN J (1867) *Zbl med Wiss* 5 1
BERNTHAL T (1932) *Amer J Physiol* 101 6
BERNTHAL, T (1934) *Amer J Physiol* 109 8
BERNTHAL T (1938) *Amer J Physiol* 121 1
BERNTHAL T (1944) *Ann Rev Physiol* 6 155
BERNTHAL, T GREENE W & REVZIN A M (1951) *Proc Soc exp biol N Y* 76 121
BERNTHAL, T MOTLEY H E SCHWIND F J & WEEKS W F (1945) *Amer J Physiol* 143 220
BERNTHAL, T & SCHWIND F J (1945) *Amer J Physiol* 143 361
BERNTHAL T & WEEKS W F (1939) *Amer J Physiol* 127 94
BERT P (1878) *La pression barometrique* Paris 1878 English translation (1943) by M A & F A Hitchcock Columbus
BEZOLD A VON (1863) *Untersuchungen uber die Innervation des Herzens* Engelmann Leipzig
BEZOLD A VON & HIRT L (1867) *Unters Physiol Lab Wurzburg* 1 73
BEYNE J GAUTRELET J & HALPERN N (1933) *C R Soc Biol Paris* 113 585
BINET L & GAYET R (1929*a*) *C R Soc Biol Paris* 100 177
BINET L & GAYET R (1929*b*) *C R Soc Biol Paris* 100 180
BINET L & GAYET R (1929*c*) *C R Soc Biol Paris* 100 338
BING R J THOMAS C B & WAPLES E C (1945) *J clin Invest* 24 513
BING R J HAMMOND M M HANDELSMAN J C POWERS S R SPENCER F C ECKENHOFF J E GOODALE W T HAFKENSCHIEL J H & KETY S S (1949) *Amer Heart J* 38 1
BINGER C A L BOYD D & MOORE R L (1927) *J exp Med* 45 643
BINGER C A L BROW G R & BRANCH A (1924) *J clin Invest* 1 127 and 155
BINSWANGER O (1879) *Arch Psychiat Nervenkr* 9 351
BISHOP E H HEINBECKER P & O LEARY J (1933) *Amer J Physiol* 109 409
BJORK V O (1954) *Acta chir scand* 107 466
BJORK, V O MALMSTROM G & UGGLA L G (1954) *Amer Heart J* 47 635
BJURSTEDT A G H (1946) *Acta physiol scand* 12 Suppl 38
BJURSTEDT A G H (1953) *Acta physiol scand* 29 145
BJURSTEDT A G H & EULER U S VON (1942) *Acta physiol scand* 4 23
BJURSTEDT A G H & HESSER C M VON (1942) *Acta physiol scand* 4 5
BLALOCK A (1940) *Physiol Rev* 20 159
BLINKS J R (1956) *Amer J Physiol* 186 299
BOAS J E V (1883) *Morph Jb* 8 169
BOELAERT R E (1948) *Arch int Pharmacodyn* 75 417
BOGUE J Y & STELLA G (1934) *J Physiol* 82 23P
BOGUE J Y & STELLA G (1935) *J Physiol* 83 459
BOLTON B CARMICHAEL E A & STÜRUP G (1936) *J Physiol* 86 83

BONVALLET M DELL P & HIEBEL G (1953) *C R Soc Biol Paris* 147, 1 162
BONVALLET M DELL P & HIEBEL G (1954) *Electroenceph clin Neurophysiol* 6 119
BONVALLET M DELL P & HUGELIN A (1954) *J Physiol Path gen* 46 262
BOOTHBY W M (1945) *Proc Mayo Clin* 20 209
BORDEN C W WILSON R H EBERT R V & WELLS H S (1950) *New Engl J Med* 242 529
BORISON H L FAIRBANKS V F & WHITE C A (1955) *Arch int Pharmacodyn* 101 189
BOSS J & GREEN J H (1956) *Circ Research* 4 12
BOTAR J (1932) Discussion on paper by Cordier & Coulouma *C R Ass Anat* 27th Reunion 177
BOUCKAERT J J & DAUTREBANDE L & HEYMANS C (1930) *J Physiol* 71 5P
BOUCKAERT J J & HEYMANS C (1930) *J Physiol* 69 254
BOUCKAERT J J DAUTREBANDE L & HEYMANS C (1931) *Ann Physiol Physicochim biol* 7 207
BOUCKAERT J J GRIMSON K S HEYMANS C & SAMAAN A (1941) *Arch int Pharmacodyn* 65 63
BOUCKAERT J J & HEYMANS C (1935) *J Physiol* 84 367
BOUCKAERT J J & JOURDAN F (1949) *J Physiol Path gen* 41 69A
BOUCKAERT J J & LEUSEN I (1951) *Arch int Pharmacodyn* 87 393
BOUCKAERT J J & PANNIER R (1942*a*) *Arch int Pharmacodyn* 67 61
BOUCKAERT J J & PANNIER R (1942*b*) *Arch int Pharmacodyn* 67 464
BOUCKAERT J J REGNIERS P & HEYMANS C (1931) *Ann Physiol Physicochim biol* 7 207
BOVET D & BOVET NITTI F (1948) *Medicaments du Système nerveux vegetatif* Karger Basel
BOXILL G C & BROWN R V (1953) *Amer J Physiol* 172 385
BOYCOTT A E & HALDANE J S (1908) *J Physiol* 37 355
BOYD J D (1936) *J Anat Lond* 71 157
BOYD J D (1937) *Contr Embryol Carneg Instn* 26 1
BOYD J D (1937) *Anat An* 84 386
BOYD J D (1939) *London Hosp Ga* 42 Suppl
BOYD J D (1941) *J Anat Lond* 75 457
BOYD J D (1942) *J Anat Lond* 76 248
BOYD J D (1952) *Visceral Circulation* (Ed Wolstenholme G E W) p 3 Churchill London
BOYD J D (1952*a*) In Hamilton Boyd & Mossman *Human Embryology* 2nd Ed Heffer Cambridge
BOYD J D & MCCULLAGH G P (1938) *Quart J exp Physiol* 27 293
BRACHET J L (1830) *Recherches experimentales sur les fonctions du système nerveux ganglionnaire* 2nd Edn p 387 Paris
BRADFORD J R (1889) *J Physiol* 10 358
BRADFORD J R & DEAN H P (1889) *Proc Roy Soc B* 45 369
BRADFORD J R & DEAN H P (1894) *J Physiol* 16 34
BRAEUCKER W (1922) *Anat An* 56 225
BRAUN L & SAMET B (1934) *Wien klin Wschr* 47 65 134
BRAUNER F BRUCKE F VON & KAINDL F (1950) *Arch int Pharmacodyn* 82 192
BRAUNER F BRUCKE F VON KAINDL F & NEUMAYER A (1951) *Arch int Pharmacodyn* 83 505
BRAUNSTEIN E P (1894) *Zur lehre von der Innervation der Pupillenbewegung* Wiesbaden
BREWER N R (1937) *Amer J Physiol* 120 91
BREWIN E G GOULD R P NASHAT F S & NEIL E (1955) *Guy's Hosp Rep* 104 177
BRIGDEN W & SHARPEY SCHAFER E P (1950) *Clin Sci* 9 93
BRODIE T G (1900) *J Physiol* 26 48
BRODIE T G & RUSSELL A E (1900) *J Physiol* 26 92
BRONK D W (1929) *J Physiol* 67 270
BRONK D W (1931) *Proc Soc exp Biol N Y* 28 1 014
BRONK D W (1933–4) *Harvey Lect* 29 545
BRONK D W FERGUSON L K MARGARIA R & SOLANDT D Y (1936) *Amer J Physiol* 117 237
BRONK D & W GESELL R (1926) *Proc Soc exp Biol N Y* 24 255
BRONK D W & GESELL R (1927) *Amer J Physiol* 82 170
BRONK D W PITTS R F & LARRABEE M G (1940) *A Res Nerv & Ment Dis Proc* 20 323
BRONK D W & STELLA G (1932) *J cell comp Physiol* 1 113
BRONK D W & STELLA G (1935) *Amer J Physiol* 110, 708
BROWN E B (1950) *J appl Physiol* 2 549
BROWN E B CAMPBELL G S JOHNSON M N HEMINGWAY A & VISSCHER M B (1948) *J appl Physiol* 1 333
BROWN G L & GRAY J A B (1948) *J Physiol* 107 306
BROWN R V & HILTON J G (1955) *Amer J Physiol* 183 137 433

BROWN R V & HILTON J G (1954a b) *Amer J Physiol* **177** 303 **178** 211
BRÜCKE E (1852) *Denkschr Akad Wiss Wien* **3** 335
BRUCKE F VON (1952) *Arch exp Path Pharmak* **215** 363
BUCY P (1936) *Arch intern Med* **63** 428
BUDDE H (1954) *Arch int Pharmacodyn* **97** 141
BUDDE H DONAT K & WITZLEB E (1955) *Arch int Pharmacodyn* **100** 479
BUDDE H & WITZLEB E (1955) *Arch int Pharmacodyn* **102** 126
BUDDE M (1926) *Z ges exp Med* **50** 207
BUDGE J L (1853) *C R Acad Sci Paris* **36** 378
BÜLBRING E & WHITTERIDGE D (1943) *J Physiol* **103** 477
BUNCH J L (1899) *J Physiol* **24** 72
BURCH G E (1954) *Arch intern Med* **94** 724
BURCH G E & ROMNEY R B (1954) *Amer Heart J* **47** 58
BURN J H (1956) *Brit J Anæsth* **28** 459
BURSTEIN C L JACKSON A & ROVENSTINE E A (1949) *Proc Soc exp biol N Y* **70** 718
BURSTEIN C L JACKSON A BISHOP H F & ROVENSTINE E A (1950) *Anæsthesiology* **11** 409
BURSTEIN M (1946) *J Physiol Path gén* **39** 75
BURTON A C (1951) *Amer J Physiol* **164** 319
BURTON A C (1953) *Ann Rev Physiol* **15** 213
BUSACHI P (1912) *Arch ital Anat Embriol* **11** 352
BUSH A D (1920) *J Pharmacol* **15** 297

CACCAMISE W C & WHITMAN J F (1952) *Amer Heart J* **44** 629
CAJAL R y (1911) *Histol du syst nerveux* Bd 2 Maloine Paris
CALDEYRO R & GARCIA AUSTT E (1949) *Arch int Pharmacodyn* **80** 89
CAMUS L BENARD H & MERKLEN F P (1934) *C R Soc Biol* Paris **115** 1 626
CANNON W B LEWIS J T & BRITTON S W (1926) *Amer J Physiol* **77** 326
CARMAN J B (1955) *J Anat Lond* **89** 503
CASHCOVSKY P E (1899) *M D Thesis* Med Acad Petrograd
CASIER H & DE VLEESCHHOUWER G R (1952) *Arch int Pharmacodyn* **90** 412
CATTELL McK (1923) *Arch Surg Chicago* **6** 41
CELANDER O (1954) *Acta physiol scand* **32** suppl 116
CELANDER O & FOLKOW B (1951) *Acta physiol scand* **23** 64
CELANDER O & FOLKOW B (1953) *Acta physiol scand* **29** 241
CELESTINO DA COSTA A (1935) *J Anat Lond* **69** 479
CELESTINO DA COSTA A (1939) *Bull Ass Anat Paris* **49** 30
CELESTINO DA COSTA A (1944) *Arch portug Sci biol* **8** Suppl
CERLETTI A LI T H ALANIS J & AVIADO D M (1951) *Fed Proc* **10** 286
CHABROL M (1927) *Des mecanismes nerveux regulateurs de la pression arterielle* Thesis Algiers
CHARLIER R (1948) *Acta cardiol* **3** 1
CHARLIER R & PHILIPPOT E (1947) *Arch int Pharmacodyn* **75** 90
CHATFIELD P O & PURPURA D P (1953) *Amer J Physiol* **172** 632
CHAUVEAU A & ARLOING S (1905) *Traite d anatomie comparee des animaux domestiques* Vol 2 5th edn Baillière Paris
CHERNIKOVSKII V N (1943) *Bull Biol Med exp* U S S R **15** 31
CHESHCOV A M (1902) *M D Thesis* Med Acad Petrograd
CHIODI H DILL D B CONSOLAZIO F & HORVATH S M (1941) *Amer J Physiol* **134** 683
CHOWDHARY D S (1951) *Nature Lond* **167** 1074
CHOWDHARY D S (1950) *Anat Rec* **107** 235
CHRISTENSEN E H (1937a) *Skand Arch Physiol* **76** 88
CHRISTENSEN E H (1937) *Ergebn Physiol* **39** 348
CHRISTENSEN E H (1954) p 103 *Handbook of Respy Physiology* U S A F Project No 21-2301-0003
CHRISTENSEN E H (1954) *Proc Roy Soc* B **143** 8
CHRISTIE R V (1938) *Quart J Med* **31** 421
CHUNGCHAROEN D (1952) *Studies on carotid circulation of various species* Ph D Thesis University of London
CHUNGCHAROEN D DALY M de B NEIL E & SCHWEITZER A (1952) *J Physiol* **117**, 56
CHUNGCHAROEN D DALY M de B & SCHWEITZER A (1952) *J Physiol* **117** 347
CHUNGCHAROEN D DALY M de B & SCHWEITZER A (1952b) *J Physiol* **118** 528

CHURCHILL E D & COPE O (1929) *J exp Med* **49** 531
CLARK B B VAN LOON E J & ADAMS W L (1943) *Amer J Physiol* **139** 64
CLARK G A (1934) *J Physiol* **83** 229
CLARK R E (1955) *Anæsthesiology* **16** 716
CODE C F DINGLE W T & MOORHOUSE V H K. (1936) *Amer J Physiol* **115,** 249
COLERIDGE J C G HEMINGWAY A HOLMES R L & LINDEN R J (1956) *J Physiol* **132** 68P
COLERIDGE J C G KENNEY R A & NEIL E (1949) *J Physiol* **110** 27P
COLERIDGE J C G & LINDEN R J (1955) *J Physiol* **128** 310
COLERIDGE J C G & LINDEN R J (1955) *J Physiol* **130** 674
COLLIP J B (1920–1) *J Physiol* **54** 58
COLLIP J B & BACKUS P L (1920) *Amer J Physiol* **51** 551
COMROE J H (1939) *Amer J Physiol* **127** 176
COMROE J H (1943) *Amer J Physiol* **139** 390
COMROE J H VAN LINGEN B STROUD R C & RONCORONI A (1953) *Amer J Physiol* **173** 379
COMROE J H & SCHMIDT C F (1938) *Amer J Physiol* **121** 75
CONCATO L (1870) *Riv clin di Bologna* **9** 1
CONCATO L (1872) *Riv clin di Bologna* 2 Ser **11** 6 and 161
CONDORELLI L (1952) *Cardiologia* **21** 379
COOPER A (1836) *Guy s Hosp Rep* **1** 457
CORDIER P & COULOUMA P (1932) *C R Ass Anat 27th Réunion* 161
CORMACK R S CUNNINGHAM D J C & GEE J B L (1955) *J Physiol* **128** 29P
CORMACK R S CUNNINGHAM D J C & GEE J B L (1956) *J Physiol* **133** 47P
CORMACK R S CUNNINGHAM D J C & GEE J B L (1957) *Quart J exp Physiol* **42** 303
CRAMER W (1915) *J Pharmacol* **7** 63
CROSS K W HOOPER J M D & LORD J M (1954) *J Physiol* **129** 29P
CROSS K W & MALCOLM J L (1952) *J Physiol* **118** P
CROSS K W & OPPÉ T E (1952*a*) *J Physiol* **116** 168
CROSS K W & OPPÉ T E (1952*b*) *J Physiol* **117,** 38
CROSS K W & WARNER P (1951) *J Physiol* **114** 283
CRUICKSHANK W (1795) *Phil Trans* p 190
CUSHING H (1902) *Amer J Med Sci* **124** 375
CUYPERS H (1935) *Arch int Pharmacodyn* **50** 226
CYBULSKI N (1895) *Zbl Physiol* **9** 172
CYON E DE (1866) *Zbl med Wiss* **4** 801
CYON E DE (1867) *Arch Anat Physiol* Lpz 403
CYON E DE (1871) *Bull Acad Sci* St Petersb **15** 262
CYON E DE (1898) *Pflug Arch ges Physiol* **70** 126
CYON E DE (1900) *Chapter Depressor in Dictionnaire de Physiologie by Ch Richet* **4** 774
CYON E DE (1906) *Les nerfs du coeur* Alcan Paris
CYON E DE & CYON M DE (1867) *Arch anat Physiol Lpz* 389
CYON E DE & LUDWIG C (1866) *Ber sachs Ges (Akad) Wiss* **18** 307

DALE H H & EVANS C L (1922) *J Physiol* **56** 125
DALY I DE B (1933) *Physiol Rev* **13** 149
DALY I DE B (1935–6) *Harvey Lect* **31** 235
DALY I DE B & DALY M DE B (1957) *J Physiol* **137** 28P
DALY I DE B & EULER U S VON (1932) *Proc Roy Soc* B **110** 92
DALY I DE B & HEBB C (1952) *Quart J exp Physiol* **37** 19
DALY I DE B LUDANY G TODD A & VERNEY E B (1937) *Quart J exp Physiol* **27** 123
DALY I DE B & VERNEY E B (1926) *J Physiol* **61** 268
DALY I DE B & VERNEY E B (1927) *J Physiol* **62** 330
DALY I DE B DUKE H N LINZELL J L & WEATHERALL J (1952) *Quart J exp Physiol* **37** 149
DALY I DE B ELSDEN S R HEBB C O LUDANY G & PETROVSKAIA B (1942) *Quart J exp Physiol* **31,** 227
DALY M DE B (1954) *Pharmacol Rev* **6** 79
DALY M DE B (1955) *J Physiol* **128** 33P
DALY M DE B AVIADO D M & LEE C Y (1953) *Proc XIX internat Physiol Congress* 298
DALY M DE B & EVANS D H L (1953) *J Physiol* **120** 579
DALY M DE B LAMBERTSEN C J & SCHWEITZER A (1954) *J Physiol* **125** 67
DALY M DE B & SCHWEITZER A (1951*a*) *Acta physiol scand* **22** 66

DALY M DE B & SCHWEITZER A (1951*b*) *J Physiol* 113 442
DALY M DE B & SCHWEITZER A (1952) *J Physiol* 116 35
DALY M DE B & SCHWEITZER A (1956) *J Physiol* 131 220
D ANGELO S (1946) *Amer J Physiol* 146 710
DANIELOPOLU D ASLAN A MARCU L PROCA G G & MANESCU E (1927) *Presse med* 35 1 585
DANIELOPOLU D & MANESCU E (1928) *Z ges exp Med* 63 143
DANIELOPOLU D MARCU L & PROCA G G (1928) *Z ges exp Med* 63 157
DANIELOPOLU D MARCU L PROCA G G & MANESCU E (1930) *Z ges exp Med* 70 268
DANIELOPOLU D MARCU L PROCA G G ASLAN A (1932) *Presse med* 40 489
DAUTREBANDE L (1937) *Vol Jub en hon du Prof J Demoor* p 133
DAUTREBANDE L & MARECHAL, R (1933) *C R Soc Biol Paris* 113 76
DAVENPORT H W BREWER G CHAMBERS A H GOLDSCHMIDT S (1947) *Amer J Physiol* 148 392 406
DAVIS D D & STORY H E (1943) *Field Mus Publ Zool* Ser 28 No 1
DAWES G S (1947) *J Pharmacol* 89 325
DAWES G S (1952*a*) *Brit Med Bull* 8 324
DAWES G S (1952*b*) *In Ciba Foundation Symposium on Visceral Circulation* Churchill London
DAWES G S (1953) *Abstr Proc XIX Internat Physiol Congress* 51
DAWES G S & COMROE J H (1954) *Physiol Rev* 34 167
DAWES G S & FASTIER F N (1950) *Brit J Pharmacol* 5 323
DAWES G S & FELDBERG W (1949) *J Physiol* 108 362
DAWES G S & MOTT J C (1950) *Brit J Pharmacol* 5 65
DAWES G S MOTT J C & WIDDICOMBE J G (1951*a*) *J Physiol* 115 258
DAWES G S MOTT J C & WIDDICOMBE J G (1951*b*) *Brit J Pharmacol* 6 675
DAWES G S MOTT J C & WIDDICOMBE J G (1952) *Arch int Pharmacodyn* 90 203
DAWES G S & WIDDICOMBE J E (1953) *Brit J Pharmacol* 8 395
DE BETTENCOURT J M & CARDOSO M R (1937) *Arch portug Sci biol* 4 155
DE BOISSEZON P (1936) *Ann Anat path med chir* 13 733
DE BOISSEZON P (1939) *J Méd Bordeaux* 13 341
DE BOISSEZON P (1942) *La zone reflexogène carotidienne* Librairie Marqueste Toulouse
DE BOISSEZON P (1943) *Biol et med* 33 34
DE BOISSEZON P (1943) *Bull Histol Tech micr* 20 136
DE BOISSEZON P (1944) *Bull Histol Tech micr* 21 54
DE BOISSEZON P (1944) *Toulouse med* 45 329
DE CASTRO F (1926) *Trab lab Invest biol Univ Madrid* 24 365
DE CASTRO F (1928) *Trab lab Invest biol Univ Madrid* 25 331
DE CASTRO F (1929) *Z ges Anat I Z Anat Entwgesch* 80 250
DE CASTRO F (1940) *Trab Lab Invest biol Univ Madrid* 32 297
DE CASTRO F (1942) *Trab Lab Invest biol Univ Madrid* 34 217
DE CASTRO F (1944) *Trab Lab Invest biol Univ Madrid* 36 345
DE CASTRO F (1951) *Acta physiol scand* 22 14
DE GRAFF A C & SANDS J (1925) *Amer J Physiol* 74 400
DE KOCK L L (1951) *Nature Lond* 167 611
DE KOCK L L (1954) *Acta anat* 21 101
DE KOCK L L (1956) *Nature Lond* 177 1084
DE MEURON P (1896) *Recueil Zool Suisse Ié serie Tome III*
DE VLEESCHHOUWER G R (1935) *Arch int Pharmacodyn* 50 251
DE VLEESCHHOUWER G R MARTINI L & CALLIAUW L (1953) *Arch int Pharmacodyn* 96 195
DE VLEESCHHOUWER G R PANNIER R & DELAUNOIS A L (1949) *C R Soc Biol Paris* 143 610
DE WAELE H & VAN DE VELDE J (1940) *Arch int Physiol* 50 33
DE WISPELAERE H (1937) *Arch int Pharmacodyn* 56 363
DELAUNOIS A L & MARTINI L (1953) *Arch int Pharmacodyn* 94 430
DELL P (1952) *J Physiol Path gen* 44 471
DELL P & BONVALLET M (1954) *C R Soc Biol* (Paris) 148 855
DELL P & BONVALLET M (1956) *Ann Rev Physiol* 18 309
DELL P & BONVALLET M (1956) *Abstr Rev XX Int Congress Physiol* 286
DELL, P BONVALLET M & HUGELIN A (1954) *Electroencephalog clin Neurophysiol* 6 599
DELMAS J & LAUX G (1933) *Anatomie medico chirurgicale du Système Nerveux vegetatif* Masson Paris
DEXTER L (1952) *Bull N Y Acad Med* 28 90

DEXTER L DOW J W HAYNES F W WHITTENBERGER J L FERRIS B G GOODALE W T & HELLEMS H K (1950*a*) *J clin Invest* 29 602
DEXTER L GORLIN R LEWIS B M HAYNES F W & HARKEN D E (1950*b*) *Trans Amer climat (clin) Ass* 62 1 050
DIAMOND J (1955) *J Physiol* 130 513
DIAMOND J & HOWE A (1955) *J Physiol* 128 76–77P
DIAMOND J & HOWE A (1956) *J Physiol* 134 319
DICKINSON E H (1929) *J Physiol* 67 242
DICKINSON C J (1950) *J Physiol* 111 399
DILL D B TALBOTT J H & CONSOLAZIO W V (1937) *J biol Chem* 118 649
DILL D B & ZAMCHECK N (1940) *Amer J Physiol* 129 47
DIRKEN M N J & HEEMSTRA H (1948) *Quart J exp Physiol* 34 193 and 227
DITTMAR C (1870) *Ber sachs Ges (Akad) Wiss* 22 18
DITTMAR C (1873) *Ber sachs Ges (Akad) Wiss* 25 449
DOGIEL A S (1898*a*) *Arch mikr Anat* 52 44
DOGIEL A S (1898*b*) *Arch mikr Anat* 53 237
DOGIEL J & ARCHANGELSKY K (1906) *Pflug Arch ges Physiol* 113, 21
DOGIEL, J (1911) *Pflug Arch ges Physiol* 142 109
DOLE V P & MORISON R S (1940) *Amer J Physiol* 130 304
DONATELLI L & SHEN T C R (1938) *Arch int Pharmacodyn* 60 331
DONDERS F (1868) *Pflug Arch ges Physiol* 1, 331
DONEGAN J F (1921) *J Physiol* 55 226
DONTAS A S (1954) *Fed Proc* 13 37
DONTAS A S (1955) *Circ Research* 3 363
DONTAS A S & NICKERSON M (1956) *Fed Proc* 13 37
DOUGLAS C G p 1 *in Handbook of Respy Physiology* U S A F Project 21-2301-0003
DOUGLAS C G & HALDANE J S (1909) *J Physiol* 38 420
DOUGLAS C G & HALDANE J S HENDERSON Y & SCHNEIDER E C (1913) *Phil Trans* 203, 85
DOUGLAS W W (1952) *J Physiol* 118 373
DOUGLAS W W (1954) *Pharmacol Rev* 6 81
DOUGLAS W W & GRAY J A B (1953) *J Physiol* 119 118
DOUGLAS W W INNES I R & KOSTERLITZ H W (1950) *J Physiol* 111 215
DOUGLAS W W RITCHIE J M & SCHAUMANN W (1956) *J Physiol* 132 187
DOUGLAS W W & SCHAUMANN W (1956) *J Physiol* 132 173
DOUGLAS W W & TOH C C (1953) *J Physiol* 120 311
DUOMARCO J L DILLON W H & WIGGERS C J (1948) *Amer J Physiol* 154 290
DRAPER A (1950) *Ann intern Med* 32 700
DRAPER W B WHITEHEAD R W SPENCER J N (1947) *Anæsthesiology* 8 524
DRIPPS R D & COMROE J H (1947) *Amer J Physiol* 149, 277
DRIPPS R D & DUMKE P R (1943) *J Pharmacol* 77 290
DRIVER R L & VOGT M (1950) *Brit J Pharmacol* 5 505
DRUNER L (1925) *Dtsch med Wschr* 51 559
DUKE H GREEN J H & NEIL E (1953) *J Physiol* 118 520
DUMKE P R & SCHMIDT C F (1941) *Amer J Physiol* 133 266
DUMKE P R & SCHMIDT C F (1943) *Amer J Physiol* 138 421
DUMKE P R SCHMIDT C F & CHIODI H (1941) *Amer J Physiol* 133 1
DURIG A KOLMER W RAINER R REICHEL H CASPARI W (1909) *Denkschr Akad Wiss Wien* 86 242

EAD H W GREEN J H & NEIL E (1952) *J Physiol* 118 509
EDHOLM O G & MCDOWALL R J S (1936) *J Physiol* 86 8P
EGBERTS M A (1932) *Carotid sinus reflex and eye reflexes in the Clinic* Thesis Amsterdam
EINBRODT M (1860) *S B Akad Wiss Wien* 40 345
EINTHOVEN W (1908) *Quart J exp Physiol* 1 243
EISEN V D & LEWIS A A G (1954) *Lancet* ii 361
ELIASSON S FOLKOW B LINDGREN P & UVNAS B (1951) *Acta physiol scand* 23 333
ELIASSON S LINDGREN P & UVNAS B (1952) *Acta physiol scand* 27 18
ELAUT L (1935) *C R Soc Biol Paris* 119 318
ELAUT L (1936) *C R Soc Biol Paris* 122 126
ELFTMANN A. G (1943) *Amer J Anat* 72 1

ELLENBERGER W & BAUM H (1891) *Anatomie des Hundes* Parey Berlin
ELLENBERGER W & BAUM H (1932) *Handbuch der vergl Anat der Haustiere* 17 ed Springer Berlin
ELLIOTT T R (1912) *J Physiol* **44** 374
ELLIS M M (1919) *Amer J Physiol* **50** 267
EMBLEY E H (1902) *Brit med J* **i** 817 885 951
ERANKO O (1955) *Nature Lond* **175** 88
ERLANGER J & GASSER H S (1937) *Electrical Signs of Nervous Activity* Oxford Univ Press London
ERDMANN W D & ROHR H (1954) *Arch int Pharmacodyn* **98** 81
ERSPAMER V (1954) *Pharmacol Rev* **6** 425
ERSPAMER V & ASERO B (1952) *Nature Lond* **169** 800
ESKUCHEN K & LICKINT F (1927) *Dtsch med Wschr* **53** 651
EULER, C VON (1949) *Acta physiol scand* **19** 62
EULER C VON & SODERBERG U (1952*a*) *J Physiol* **118** 545
EULER C VON & SODERBERG U (1952*b*) *J Physiol* **118** 555
EULER U S VON (1946) *Acta physiol scand* **11** 168
EULER U S VON (1946) *Acta physiol scand* **12** 73
EULER U S VON (1948) *Acta physiol scand* **16** 63
EULER U S VON (1948) *Science* **107** 422
EULER U S VON (1950) *Ergebn Physiol* **46** 261
EULER U S VON (1951*a*) *Brit med J* **20/1** 105
EULER U S VON (1951*b*) *Pharmacol Rev* **3** 247
EULER U S VON (1956) *Noradrenaline* Thomas Springfield Ill
EULER U S VON & FOLKOW B (1951) *Amer J Physiol* **166** 284
EULER U S VON & FOLKOW B (1953) *Arch exp Path Pharmak* **219** 242
EULER U S VON & LILJESTRAND G (1934) *Skand Arch Physiol* **71** 73
EULER U S VON & LILJESTRAND G (1936) *Skand Arch Physiol* **74** 101
EULER U S VON & LILJESTRAND G (1937*a*) *Skand Arch Physiol* **76** 27
EULER U S VON & LILJESTRAND G (1937*b*) *Skand Arch Physiol* **77** 191
EULER U S VON & LILJESTRAND G (1940) *Acta physiol scand* **1** 93
EULER U S VON & LILJESTRAND G (1941) *Acta physiol scand* **1** 383
EULER U S VON & LILJESTRAND G (1942) *Acta physiol scand* **4** 34
EULER U S VON & LILJESTRAND G (1943) *Acta physiol scand* **6** 319
EULER U S VON & LILJESTRAND G (1946) *Acta physiol scand* **12** 301
EULER U S VON LILJESTRAND G & ZOTTERMAN Y (1939) *Skand Arch Physiol* **83** 132
EULER U S VON LILJESTRAND G & ZOTTERMAN Y (1941) *Acta physiol scand* **2** 1
EULER U S VON & SCHMITERLOW C G (1944) *Acta physiol scand* **8** 122
EULER U S VON & ZOTTERMAN Y (1942) *Acta physiol scand* **4** 13
EVANS C H (1928) *Amer J Surg* **5** 581
EYSTER J A E (1906) *J exp Med* **8** 565
EYSTER J A E BURROWS M T & ESSICK C R (1909) *J exp Med* **11** 490
EYSTER J A E & HOOKER D R (1907) *Zbl Physiol* **21** 615
EYSTER J A E & HOOKER D R (1908) *Amer J Physiol* **21** 373

FABINYI M & SZEBEHELYI J (1948) *Arch int Pharmacodyn* **76** 397
FARBER S J BECKER W H & EICHNA L W (1953) *J clin Invest* **32** 1145
FASTIER F N (1955) *Proc Univ Otago Med School* **33** 35
FASTIER F N WAAL H & WONG L C K (1957) *Proc Univ Otago Med School* **35** 1
FEFJAR Z (1950) *Proc XVIII Internat Physiol Congress* 196
FELIX W (1955) *Arch exp Path Pharmak* **225** 152
FERNANDEZ A (1949) *Arch int Pharmacodyn* **80** 82
FERNANDEZ E & CERLETTI A (1955) *Arch int Pharmacodyn* **101** 425
FERRIS E B CAPPS R B & WEISS S (1935) *Medicine* **14** 377
FINKELSTEIN A (1880) *Arch Anat Physiol Lpz* 245
FISCHELIS PH (1885) *Arch mikr Anat* **25** 405
FISCHER M H GANTT J & LOWENBACH H (1933) *Pflug Arch ges Physiol* **233** 732
FISCHER M H & LOWENBACH H (1933) *Pflug Arch ges Physiol* **233** 722
FISCHER W (1924) *Z ges exp Med* **39** 477
FITZGERALD M P (1913) *Phil Trans Roy Soc B* **203** 351
FLEISCH A (1929) *Amer J Physiol* **90** 346
FLEISCH A (1930) *Pflug Arch ges Physiol* **225** 26

FLEISCH A (1930) *Pflug Arch ges Physiol* **226** 393
FLOREY H MARVIN H M & DRURY A N (1928) *J Physiol* **65** 204
FLOURENS J P M (1824) *Recherches experimentales sur les propriétés et les fonctions du système nerveux dans les animaux vertebres* Crevot Paris
FLOYD W F & NEIL E (1952) *Arch int Pharmacodyn* **91** 230
FOA C (1913) *Pflug Arch ges Physiol* **153** 513
FOA C (1921) *Arch int Physiol* **17** 229 and **18** 391
FOFANOW W L L & TSCHALUSSOW M A (1913) *Pflug Arch ges Physiol* **151** 543
FOLKOW B (1952) *Acta physiol scand* **25** 49
FOLKOW B (1953) *Acta physiol scand* **27**, 99
FOLKOW B (1955) *Physiol Rev* **35** 629
FOLKOW B (1956) *Ann Rev Physiol* **18** 159
FOLKOW B & VON EULER U S (1954) *Circ Research* **2** 191
FOLKOW B STROM G & UVNAS B (1949) *Acta physiol scand* **17** 327
FOLKOW B STROM G & UVNAS B (1950) *Acta physiol scand* **21** 145
FOLKOW B & UVNAS B (1948) *Acta physiol scand* **15** 389
FOLKOW B & UVNAS B (1950) *Acta physiol scand* **20** 329
FONTAINE R HOERNER G & MANDEL, P (1938) *Arch Mal coeur* **64** 1090
FONTAINE R & MANDEL P (1938) *C R Soc Biol Paris* **127** 448
FORBES H S (1940) *Arch Neurol Psychiat Chicago* **43** 804
FOWLER N O WESTCOTT R N & SCOTT R C (1952) *J clin Invest* **31** 72
FOWLER N O WESTCOTT R N HAUENSTEIN V D SCOTT R C & MCGUIRE J (1950) *J clin Invest* **29** 1387
FOWLER W S (1954) *J appl Physiol* **6** 539
FRANCOIS FRANCK C A (1877) *Trav lab Marey* **3** 273
FRANCOIS FRANCK C A (1878) *Trav lab Marey* **4** 281
FRANCOIS FRANCK C A (1892) *Arch physiol norm path* **2** 546
FRANCOIS FRANCK C A (1899) *J Physiol Path gén* **1** 753
FRANCOIS FRANCK C A & HALLION L (1896) *Arch physiol norm path* **28** 478
FRANKLIN K J (1928) *Physiol Rev* **8** 346
FRANKLIN K J (1931) *Proc R Soc Med* **25** 113
FRANKLIN K J (1937) *A monograph on veins* Thomas Baltimore
FREDERICQ L (1882) *Arch Biol Paris* **3** 55
FREDERICQ L (1887) *Bull acad Belg Cl Sci* **13** 417
FREDERICQ L (1889) *Trav lab Physiol Liege* **3** 1
FREDERICQ L (1890) *Arch Biol Paris* **10** 127
FREDERICQ L (1897) *Dictionnaire de Physiologie* (Ch Richet) *p* 455
FREDERICQ L (1901) *Arch Biol Paris* **17** 561
FREUNDLICH L (1930) *Dtsch Arch Klin Med* **168** 390
FRUMIN M J NAGAI S H & WANG S C (1953) *Amer J Physiol* **173** 428
FUCHS S (1897) *Pflug Arch ges Physiol* **67** 117
FUKUDA T & KUSHIYAKI K (1951) *Kyushu mem Med Sci* **2** 137
FUSARI A (1891) *Arch ital Biol* **16** 262

GAISBOCK F (1928) *Ber uber die Sitzung d wiss Arztgesellschaft Innsbruck* 71
GALLEOTTI G (1904) *Arch ital Biol* **41** 80
GAMMON G D BRONK D W (1935) *Amer J Physiol* **114** 77
GASKELL P & BURTON A C (1953) *Circ Research* **1** 27
GASKELL, W H (1878) *J Physiol* **1** 108 262
GASKELL W H & GADOW H (1883) *J Physiol* **5** 362
GASSER H & GRUNDFEST H (1939) *Amer J Physiol* **127** 393
GASSER H S & LOEVENHART A S (1914) *J Pharmacol* **5** 239
GAUER O H (1955) *Physiol Rev* **35** 143
GAUER O H HENRY J P SIEKER H O (1956) *Circ Research* **4** 79
GAUER O H HENRY J P SIEKER H O & WENDT W I (1954) *J clin Invest* **33** 287
GAYET R BENNATI D & QUIVY D (1935) *Arch int Pharmacodyn* **50** 129
GAYET R GAYET T & QUIVY D (1933) *C R Soc Biol Paris* **114** 619
GAYLOR N B (1934) *Brain* **57** 143
GELLHORN E INGRAHAM R C & MOLDAVSKY L (1938) *J Neurophysiol* **1** 301
GELLHORN E & LAMBERT E, (1939) *The vasomotor system in anoxia and asphyxia* Univ of Illinois Press

GELLHORN E REDGATE E & SIGG E (1952) *Fed Proc* **12** 50
GELLHORN E YESINICK L KESSLER M & HAILMAN H (1942) *Amer J Physiol* **137** 396
GEMMILL, C L OVERSTREET E W & HELLMAN L M (1933) *Amer J Physiol* **105** 36
GEMMILL, C L & REEVES D L (1933) *Amer J Physiol* **105** 487
GEPPERT J & ZUNTZ N (1888) *Pflug Arch ges Physiol* **42** 189
GERARD M W & BILLINGSLEY P R (1923) *Anat Rec* **25** 391
GERNANDT B E (1946) *Acta physiol scand* **11** suppl 35
GERNANDT B E LILJESTRAND G & ZOTTERMAN Y (1945) *Acta physiol scand* **9** 367
GERNANDT B E LILJESTRAND G & ZOTTERMAN Y (1946) *Acta physiol scand* **11** 230
GERNANDT B E & ZOTTERMAN Y (1946) *Acta physiol scand* **11** 301
GESELL R (1923) *Amer J Physiol* **66** 5
GESELL R (1925) *Physiol Rev* **5** 551
GESELL R (1928) *Amer J Physiol* **86** 164
GESELL R (1929) *Ergebn Physiol* **28** 340
GESELL R BRASSFIELD H & HAMILTON M A (1942) *Amer J Physiol* **136** 604
GESELL R & BRONK D W (1927) *Amer J Physiol* **79** 61
GESELL R & HERTZMANN A B (1926) *Amer J Physiol* **78** 610
GESELL R LAPIDES J & LEVIN M (1940) *Amer J Physiol* **130** 155
GESELL R & MOYER C (1937) *Amer J Physiol* **119** 55
GIGON A & LUDWIG E (1912) *Arch exp Path Pharmak* **69** 268
GILLIATT R W (1947) *J Physiol* **107** 76
GILLIATT R W GUTTMANN L & WHITTERIDGE D (1947) *J Physiol* **107** 67
GILMORE H R KOPELMAN H MCMICHAEL J & MILNE I G (1952) *Lancet* 898
GINZEL, K H & KOTTEGODA S R (1954) *J Physiol* **123** 277
GIRLING F (1952) *Amer J Physiol* **171** 204
GLEY E & QUINQUAUD A (1918) *J Physiol Path gen* **17** 807
GLEY E & QUINQUAUD A (1923) *Skand Arch Physiol* **43** 316
GOETZ R H (1935) *Pflug Arch ges Physiol* **235** 271
GOLDBLATT H (1937) *Ann intern Med* **11** 69
GOLDBLATT H LYNCH J HANZAL R F & SUMMERVILLE W W (1934) *J exp Med* **59** 347
GOLLWITZER MEIER K (1929) *Verh dtsch ges inn Med* **41** 361
GOLLWITZER MEIER K (1932) *Ergebn Physiol* **34** 1145
GOLLWITZER MEIER K (1934) *Pflug Arch ges Physiol* **234** 342
GOLLWITZER MEIER K (1942) *Luftfahrtmedi in* **6** 296
GOLLWITZER MEIER K & LERCHE E (1940) *Pflug Arch ges Physiol* **244** 145
GOLLWITZER MEIER K & SCHULTE H (1931) *Pflug Arch ges Physiol* **229** 264
GOLLWITZER MEIER K & SCHULTE H (1932) *Arch exp Path Pharmak* **165** 685
GOLLWITZER MEIER K & WITZLEB E (1953) *Pflug Arch ges Physiol* **256** 381
GOLTZ F (1863) *Virchow s Arch* **26** 1
GOLTZ F (1863) *Zbl med Wiss* **1** 593
GOLTZ F (1864) *Virchow s Arch* **29** 11 and 394
GOODRICH E S (1930) *Studies on the structure and development of vertebrates* Macmillan London
GOORMAGHTIGH N (1931) *Ann Anat path med chir* **8** 585
GOORMAGHTIGH N & ELAUT L (1929) *C R Soc Biol Paris* **101** 501
GOORMAGHTIGH N & GRIMSON K S (1939) *Proc Soc exp Biol N Y* **42** 227
GOORMAGHTIGH N & PANNIER R (1939) *Arch Biol Paris* **50** 455
GORLIN R & LEWIS B M (1954) *J appl Physiol* **7** 180
GOTO Y (1954) *Arch int Physiol* **62** 445
GOVAERTS P (1936) *C R Soc Biol Paris* **122** 449
GRAY J A B (1956) *Abstr Rev XX Internat Congress Physiol* 59
GRAY J S (1950) *Pulmonary Ventilation and its Physiological Regulation* Thomas Springfield Ill
GRAY J S & GRODINS F S (1951) *Ann Rev Physiol* **13** 217
GREBENKINA M A (1953) *Sechenov J Physiol* **39** 591
GREEN M F & DE GROAT A F (1935) *Amer J Physiol* **112** 488
GREEN M F DE GROAT A F & MCDONALD C H (1934) *Amer J Physiol* **110** 513
GREEN J H (1953) *J Physiol* **122** 70P
GREEN J H (1954) *J Physiol* **123** 41P
GREEN J H (1954) *Baroceptor and Chemoceptor Control of the Circulation* Ph D Thesis University of London
GREEN J H (1954) *J Physiol* **124** 43P

GREEN J H & NEIL E (1955) *J Physiol* **129** 134
GREENE D G & BUNNELL I L (1950) *J clin Invest* **29**, 818
GREGG D E (1950) *Coronary circulation in health and disease* Lea & Febiger Philadelphia
GREGG D E & SHIPLEY R E (1944) *Amer J Physiol* **141** 382
GRIMSON K S (1940) *Proc soc exp biol N Y* **44** 219
GRIMSON K S (1941) *Arch Surg Chicago* **43** 284
GRIMSON K S & SHEN T C R (1939) *Arch int Pharmacodyn* **63** 95
GRUHZIT C C FREYBURGER W A & MOE G K (1953) *J Pharmacol* **109** 261
GRUHZIT C C FREYBURGER W A & MOE G K (1954) *J Pharmacol* **112** 138
GRUHZIT C C & MOE G K (1949) *J Pharmacol* **96** 38
GRUHZIT C C & MOE G K (1952) *Amer J Physiol* **171** 730
GRUHZIT C C & MOE G K (1953) *Fed Proc* **12** 326
GRUHZIT C C & MOE G K (1953) *Abstr XIX Internat Physiol Congress* 419
GRUNDFEST H (1940) *Ann Rev Physiol* **2** 213
GRUTZNER P & HEIDENHAIN R (1878) *Pflug Arch ges Physiol* **16** 47
GUERNSEY C M WEISMAN S A & SCOTT F H (1933) *Arch int Med* **52** 306
GUYTON A C BATSON H M SMITH C M & ARMSTRONG G G (1951) *Amer J Physiol* **164** 360
GUYTON A C LINDSEY A W & GILLULLY J J (1954) *Circ Research* **2** 326

HADDY F J FERRIN A L HANNON D W ALDEN J F ADAMS W L & BARONOFSKY I D (1953) *Circ Research* **1** 219
HADDY F J & GILBERT R P (1956) *Circ Research* **4** 25
HAGGARD H W & HENDERSON Y (1920) *J biol Chem* **43** 3 15 and 29
HAIGHTON J (1795) *Phil Trans* **177**
HALDANE J B S (1921) *J Physiol* **55** 265
HALDANE J B S LINDER G C HILTON R & FRASER F R (1928) *J Physiol* **65** 412
HALDANE J S (1905) *J Hyg Camb* **5** 503
HALDANE J S (1922) *Respiration* Yale Univ Press New Haven
HALDANE J S (1927) *Physiol Rev* **7** 363
HALDANE J S KELLAS A M & KENNAWAY E. L (1919) *J Physiol* **53** 181
HALDANE J S & PRIESTLEY J G (1905) *J Physiol* **32** 225
HALDANE J S & PRIESTLEY J G (1935) *Respiration* Yale Univ Press New Haven
HALDANE J S & SMITH J L (1893) *J Path Bact* **1**, 168 318
HALES S (1733) *Statical Essays* Vol 2 Woodward London
HALLER A VON (1762) *Elementa physiologiae corporis humani* T IV p 256 D Arnay Lausanne
HALLION L & FRANCOIS FRANCK C A (1896) *Arch Physiol* **8** 493
HALLION L (1911) *J Physiol Path gén* **13** 881
HALMAGYI D FELKAI B IVANYI J & HETENYI G (1952) *Brit Heart J* **14** 101
HALMAGYI D FELKAI B IVANYI J ZSOTER T TENYI M & SZUCS Z (1953) *Brit Heart J* **15** 15
HALPERN B N BOUCHET N DU & NEVEU T (1954) *C R Soc Biol Paris* **148** 1172
HAMILTON W F (1955) *Physiol Rev* **35**, 161
HAMILTON W F & REMINGTON J W (1947) *Amer J Physiol* **148** 14
HAMILTON W F WOODBURY R A & VOGT E (1939) *Amer J Physiol* **125** 130
HAMILTON W J BOYD J D & MOSSMAN H W (1952) *Human Embryology* 2nd edn Heffer Cambridge
HAMMER G & MIES H (1929) *Krankheitsforschung* **7** 257
HAMMOND W S (1941) *Amer J Anat* **69** 265
HARREVELD A VAN & MCRARY W L (1940) *Proc soc exp biol N Y* **43** 564
HARRINGTON D W (1898) *Amer J Physiol* **1** 393
HARRISON T R CALHOUN J A CULLEN G E WILKINS W E & PILCHER C (1932) *J clin Invest* **11** 133
HARRISON T R HARRISON W G & MARSH J P (1932) *Amer J Physiol* **100** 417
HARRISON W G CALHOUN J A MARSH J P & HARRISON T R (1934) *Arch intern Med* **53** 561
HARTWICH A & HESSEL G (1931) *Z ges exp Med* **76** 263
HASSELBALCH K (1912) *Biochem Z* **46** 403
HASSELBALCH K A & LINDHARD J (1915) *Biochem Z* **68** 295
HATCHER R A & WEISS S (1922) *Arch intern Med* **29** 690
HATCHER R A & WEISS S (1924) *J Pharmacol* **22** 139
HAUSS W H KREUZIGER H & ASTEROTH H (1949) *Z Kreisl Forsch* **38** 28
HAZARD R CORTEGGIANI E & RENIER CORNEC A (1953) *Arch int pharmacodyn* **95** 184

HÉDON E (1910) *Arch int Physiol* 10 192
HEERDT P F & KRUGSMAN B J (1939) *Z vergl Physiol* 27 29
HEGER P (1887) *Beitr Phys Ludwig gewidmet* 193
HEIDENHAIN R (1870) *Pflug Arch ges Physiol* 3 505
HEINBECKER P (1930) *Amer J Physiol* 93 284
HEINBECKER P & O LEARY J (1933) *Amer J Physiol* 106 623
HEINEMAN E (1943) *Acta physiol scand* 6 333
HELLEMS H K HAYNES F W & DEXTER L (1948) *Amer J Physiol* 155 98
HELLEMS H K HAYNES F W & DEXTER L (1949) *J Appl Physiol* 2 24
HENDERSON L J (1909) *Ergebn Physiol* 8 254
HENDERSON Y (1919) *Science* 49 431
HENDERSON Y (1938) *Adventures in respiration* Williams & Wilkins Baltimore
HENDERSON Y & HAGGARD H W (1918) *J biol Chem* 33 333 345 and 355
HENIUS J (1930) *Klin Wschr* 9 1360
HENLE J (1841) *Allgemeine Anatomie* Voss Leipzig
HENLE J (1865) *Zeit Rat Med* 24 143
HENRY E W (1952) *Brit Heart J* 14 406
HENRY J P GAUER O H & REEVES J L (1956) *Circ Research* 4 85
HENRY J P GAUER O H & SIEKER H O (1956) *Circ Research* 4 91
HENRY J P & PEARCE J (1956) *J Physiol* 131 572
HERING E & BREUER J (1868) *S B Akad Wiss Wien* 57 673 Abt III
HERING E (1871) *S B Akad Wiss Wien* 64 (2) 333
HERING H E (1920) *Munch med Wschr* 67 28
HERING H E (1923) *Verh dtsch Ges inn Med* 35 93
HERING H E (1923) *Munch med Wschr* 70 859
HERING H E (1923) *Munch med Wschr* 70 1287
HERING H E (1924) *Munch med Wschr* 71 701
HERING H E (1924) *Pflug arch ges Physiol* 206 721
HERING H E (1924a) *Pflug Arch ges Physiol* 203 512
HERING H E (1924b) *Munch med Wschr* 71 1265
HERING H E (1925) *Dtsch med Wschr* 51 1140
HERING H E (1927) *Die Karotissinus reflexe auf Herz und Gefässe* Steinkopff Leipzig
HERING H E (1930) *Z Kreisl Forsch* 22 593
HERING H E (1932) *Der Blutdruck uglertonus in seiner Bedeutung fur den Parasympathikustonus und Sympathikustonus* Thieme Leipzig
HERMAN H MORIN G & VIAL J (1936) *Arch int Pharmadocyn* 43 23
HERTZMANN A B & DILLON J B (1939) *Amer J Physiol* 127 671
HESS F O (1925) *Munch med Wschr* 72 709
HESS W R (1926) *Pflug Arch ges Physiol* 213 163
HESS W R (1930) *Die Regulierung des Blutkreislaufes* Thieme Leipzig
HESSER C M VON (1949) *Acta physiol scand* 18 Suppl 64
HEYMANS C (1928) *Amer J Physiol* 85 498
HEYMANS C (1929a) *C R Soc Biol Paris* 100 196
HEYMANS C (1929b) *C R Soc Biol Paris* 100 199
HEYMANS C (1929c) *Arch int Pharmacodyn* 35 269 and 307
HEYMANS C (1929d) *Le sinus carotidien* H K Lewis London
HEYMANS C (1930) *Arch int Pharmacodyn* 39 334
HEYMANS C (1938) *Surgery* 4 487
HEYMANS C (1950a) *Acta physiol scand* 22 4
HEYMANS C (1950b) *Introduction to the regulation of blood pressure and heart rate* Thomas Springfield Ill
HEYMANS C (1952) *Arch exp Path Pharmak* 216 114
HEYMANS C (1953) *Acta physiol scand* 29 72
HEYMANS C (1955) *Pharmacol Rev* 7 119
HEYMANS C (1956) *Proc IInd European Congress Cardiology* 134
HEYMANS C & BAYLESS F (1937) *Arch int Pharmacodyn* 56 419
HEYMANS C & BOUCKAERT J J (1928) *C R Soc Biol Paris* 99 1871
HEYMANS C & BOUCKAERT J J (1929) *C R Soc Biol Paris* 100 202
HEYMANS C & BOUCKAERT J J (1929) *C R Soc Biol Paris* 103 31
HEYMANS C & BOUCKAERT J J (1930) *J Physiol* 69 254

HEYMANS C & BOUCKAERT J J (1931) *C R Soc Biol Paris* 106 471
HEYMANS C & BOUCKAERT J J (1932) *C R Soc Biol Paris* 110 996
HEYMANS C & BOUCKAERT J J (1933) *C R Soc Biol Paris* 113 912
HEYMANS C & BOUCKAERT J J (1934) *La sensibilite reflexogene des vaisseaux aux excitants chimiques* Hermann Paris
HEYMANS C & BOUCKAERT J J (1934) *Arch int Pharmacodyn* 48 191
HEYMANS C & BOUCKAERT J J (1938) *Ann Physiol Physicochim biol* 14 556
HEYMANS C & BOUCKAERT J J (1939) *Ergebn Physiol* 41 28
HEYMANS C & BOUCKAERT J J (1941) *Arch int Pharmacodyn* 65 196
HEYMANS C BOUCKAERT J J & BERT P (1932) *See Heymans et al (1933) p* 225
HEYMANS C BOUCKAERT J J & DAUTREBANDE L (1930*a*) *Arch int Pharmacodyn* 39 400
HEYMANS C BOUCKAERT J J & DAUTREBANDE L (1930*b*) *C R Soc Biol Paris* 105 217 and 881
HEYMANS C BOUCKAERT J J & DAUTREBANDE L (1931*a*) *C R Soc Biol Paris* 106 48
HEYMANS C BOUCKAERT J J & DAUTREBANDE L (1931*b*) *Arch int Pharmacodyn* 40 54
HEYMANS C BOUCKAERT J J & DAUTREBANDE L (1931*c*) *Arch int Pharmacodyn* 40 292
HEYMANS C BOUCKAERT J J & DAUTREBANDE L (1931*d*) *Arch int Pharmacodyn* 41 261
HEYMANS C BOUCKAERT J J EULER U S von & DAUTREBANDE L (1932) *Arch int Pharmacodyn* 43 86
HEYMANS C BOUCKAERT J J FARBER S & HSU F J (1936*a*) *Arch int Pharmacodyn* 54 129
HEYMANS C BOUCKAERT J J FARBER S & HSU F J (1936*b*) *Amer J Physiol* 117 619
HEYMANS C BOUCKAERT J J & PANNIER R (1944) *Bull Acad Med Belg* 9, 42
HEYMANS C BOUCKAERT J J & REGNIERS P (1933) *Le sinus carotidien et la zone homologue cardio-aortique* Doin Paris
HEYMANS C BOUCKAERT J J & SAMAAN A (1934) *Arch int Pharmacodyn* 48 457
HEYMANS C BOUCKAERT J J & WIERZUCHOWSKI M (1937) *Arch int Pharmacodyn* 55 233
HEYMANS C CALDEYRO R & GARCIA AUST E (1949) *Arch int Pharmacodyn* 79 466
HEYMANS C & DELAUNOIS A L (1951) *Science* 114 546
HEYMANS C & DELAUNOIS A L (1953) *Arch int Pharmacodyn* 96 99
HEYMANS C & DELAUNOIS A L (1955) *Proc Soc exp biol N Y* 89 597
HEYMANS C DELAUNOIS A L & HEUVEL HEYMANS G VAN DEN (1953) *Circ Research* 1 3
HEYMANS C DELAUNOIS A L MARTINI L & JANSSEN P (1953) *Arch int Pharmacodyn* 96 209
HEYMANS C DELAUNOIS A L & ROVATI A L (1957) *Arch int Pharmacodyn* 109 245
HEYMANS C & HEUVEL HEYMANS G VAN DEN (1950) *Arch int Pharmacodyn* 83 519
HEYMANS C & HEUVEL HEYMANS G VAN DEN (1951) *Circulation* 4 581
HEYMANS C & HEUVEL HEYMANS G VAN DEN (1953) *Arch int Pharmacodyn* 93 95
HEYMANS C HYDE J & TERP P (1951) *Arch int Pharmacodyn* 86 220
HEYMANS C HYDE J TERP P & DE VLEESCHHOUWER G R (1952) *Arch int Pharmacodyn* 90 140
HEYMANS C & JACOB J (1947) *Arch int Pharmacodyn* 75 111
HEYMANS C & LADON A (1924) *C R Soc Biol Paris* 90 966
HEYMANS C & LADON A (1925) *Arch int Pharmacodyn* 30 415
HEYMANS C & MAZZELLA H (1952) *Arch exp Path Pharmak* 215 100
HEYMANS C & PANNIER R (1946) *Proc soc exp Biol N Y* 62 228
HEYMANS C POCHET A & VAN HOUTTE H *Arch int Pharmacodyn* 104 293
HEYMANS C & REGNIERS P (1929) *Arch int Pharmacodyn* 36 116
HEYMANS C & REGNIERS P & BOUCKAERT J J (1930) *Arch int Pharmacodyn* 39 213
HEYMANS C & RIJLANT P (1933) *C R Soc Biol Paris* 11³ 69
HEYMANS C SCHAEPDRIJVER A DE & KING T O (1956) *Abstr Proc XX Internat Congress Physiol* 424
HEYMANS C SCHAEPDRIJVER A DE & KING T O (1956) *Arch int Pharmacodyn* 107 479
HEYMANS C VERBEKE R & VOTAVA Z (1948) *Arch int Pharmacodyn* 77 486
HEYMANS C & VLEESCHHOUWER G R DE (1950) *Arch int Pharmacodyn* 84 401
HEYMANS C & VLEESCHHOUWER G R DE (1950) *Arch int Pharmacodyn* 84 408
HEYMANS C & VLEESCHHOUWER G R DE (1952) *Cardiologia* 21 246
HEYMANS C & VLEESCHHOUWER G R DE (1956) *Ann Rev Physiol* 18 387
HEYMANS C & VLEESCHHOUWER G R DE & HEUVEL HEYMANS G VAN DEN (1951) *Arch int Pharmacodyn* 85 188
HEYMANS J F & HEYMANS C (1926) *C R Soc Biol Paris* 94 1255
HEYMANS J F & HEYMANS C (1926) *C R Soc Biol Paris* 95 1118
HEYMANS J F & HEYMANS C (1926) *Arch int Pharmacodyn* 32 9
HEYMANS J F & HEYMANS C (1927) *Arch int Pharmacodyn* 33 273

HEYMANS J F & HEYMANS C (1927) *C R Soc Biol Paris* **96** 716
HEYMANS J F & HEYMANS C (1928) *Arch Sci biol Napoli* **12** 153
HILL A V LONG C N H & LUPTON H (1924) *Proc Roy Soc B* **97** 155
HILL, L. (1895) *J Physiol* **18** 15
HILL, L (1896) *The Physiology and pathology of the cerebral circulation* Churchill London
HILL, L (1900) *Mechanism of the circulation of the blood* in *Text book of Physiology* edited by E A Schafer Vol 2, p 1 Young J Pentland Edinburgh and London
HILL, L & BARNARD H (1897) *J Physiol* **21** 323
HILL, L. & GREENWOOD M (1906) *Proc Roy Soc B* **77** 442
HILTON R & EICHHOLTZ F (1925) *J Physiol* **59** 413
HIROHATA S & HASHIMOTO K (1936) *Tohoku J exp Med* **28** 231 245
HIRSCH C & STADLER E (1904) *Dtsch Arch Klin Med* **81** 383
HOBBS L S HYDER R I & MCDOWALL R J S (1926) *J Physiol* **61** 19P
HOERNER G FONTAINE R & MANDEL, P (1938) *Arch Mal Coeur* **64** 1090
HOFF H E & BRECKENRIDGE C G (1955) Ch 43 *Regulation of Respiration* in *Textbook of Physiology* ed Fulton Saunders London
HOFMANN P (1929) *Amer J Physiol* **90** 393
HOLLINSHEAD W H (1937) *J comp Neurol* **67** 133
HOLLINSHEAD W H (1939) *J comp Neurol* **71** 417
HOLLINSHEAD W H (1940) *Quart Rev Biol* **15** 156
HOLLINSHEAD W H (1942) *Anat Rec* **84** 1
HOLLINSHEAD W H (1943) *Amer J Anat* **73** 185
HOLLINSHEAD W H (1945) *Anat Rec* **92** 255
HOLLINSHEAD W H & SAWYER C (1945) *Amer J Physiol* **144** 79
HOLMES R & TORRANCE R W (1955) *J Physiol* **130** 45 P
HOLMES W (1950) *Microt Vademecum* 537
HOLT J P & KNOEFEL P K (1944) *J clin Invest* **23** 657
HOLT J P RASHKIND W J BERNSTEIN F & GREISEN J C (1945) *Amer J Physiol* **146** 410
HOLTMEIER O (1927) *Munch med Wschr* **74** 682
HOLTZ P & SCHÜMANN H J (1949) *Arch exp Path Pharmak* **206** 49
HOOKER J M (1918) *Amer J Physiol* **46** 591
HOOKER J M (1921) *Physiol Rev* **1** 112
HORVATH S M DILL D B & CORWIN W (1943) *Amer J Physiol* **138** 659
HOUGH T (1895) *J Physiol* **18** 161
HOUSTON C S & RILEY R L (1947) *Amer J Physiol* **149** 565
HOVELACQUE A MAES J BINET L & GAYET R (1930) *Press med* **38** 449
HOWARD P & LEATHART G L (1951) *Clin Sci* **10** 521
HOWARTH S MCMICHAEL J & SHARPEY SCHAFER E P (1946) *Clin Sci* **6** 41
HOWE A (1956) *J Physiol* **134** 311
HUGGETT A ST G & MELLANBY J (1924) *J Physiol* **59** 387
HUNT R (1899) *Amer J Physiol* **2** 395
HUNT R & HARRINGTON D W (1897) *J exp Med* **2** 725
HURSH J B (1939) *Amer J Physiol* **127** 131
HUSCHKE E (1831) *Z Physiol* **4** 113
HYRTL, J (1838) *Ill Med Jb ost Staates* 25

INABA T (1931) *Tohoku J exp Med* **18** 185
IONESCU D & ENACHESCU M (1928) *Z ges Anat I Z Anat EntwGesch* **85** 476
IRVINE L SOLANDT D Y & SOLANDT O M (1935) *J Physiol* **84** 187
ITO T (1950) *Folia anat jap* **23** 117
IZQUIERDO J (1930*a*) *C R Soc Biol* Paris **104** 487
IZQUIERDO J (1930*b*) *Z ges exp Med* **72** 415
IZQUIERDO J (1930*c*) *J Physiol* **70** 221
IZQUIERDO J & KOCH E (1930) *Z Kreisl Forsch* **22** 735
IWASE Y & YAMANOUCHI T (1951) *Some Researches in Biophysics* *Mon Series Res Inst Appl Electricity* **2** 31

JACOBOVICI J NITZESCU I I & POP A (1928) *C R Soc Biol Paris* **98** 732
JABOBOVICI J NITZESCU I I & POP A (1929) *Z ges exp Med* **66** 359
JACOBS H I ROSEN V & AGRESS C M (1953) *Circ Research* **1** 466

JACOBS M H (1920*a*) *Amer J Physiol* 51 321
JACOBS M H (1920*b*) *Amer J Physiol* 53 457
JACOBY M (1895) *Studien z Entwicklungsgeschichte der Halsorgane der Saugethiere und des Menschen* Inaug Diss Berlin
JANSEN W H TAMS W ACHELIS H (1924) *Dtsch Arch Klin Med* 144 1
JARISCH A (1925) *J Physiol* 60 419
JARISCH A (1928) *Dtsch med Wschr* 54 1171 and 1211
JARISCH A (1938) *Wien Klin Wschr* 51 1
JARISCH A (1940) *Arch Kreislforsch* 7 260
JARISCH A (1940) *Arch Kreislforsch* 9 1
JARISCH A (1941) *Klin Wschr* 20 1 045
JARISCH A (1941) *Arch exp Path Pharmak* 197 266
JARISCH A (1949) *Wien klin Wschr* 61 555
JARISCH A & HEUZE C (1937) *Arch exp Path Pharmak* 187 706
JARISCH A LANDGREN S NEIL E & ZOTTERMAN Y (1952) *Acta physiol scand* 25 195
JARISCH A & LUDWIG W (1926) *Arch exp Path Pharmak* 114 240
JARISCH A & RICHTER H (1939*a*) *Klin Wschr* 18 185
JARISCH A & RICHTER H (1939*b*) *Arch exp path Pharmak* 193 347
JARISCH A & RICHTER H (1939*c*) *Arch exp Path Pharmak* 193 355
JARISCH A & ZOTTERMAN Y (1948) *Acta physiol scand* 16 31
JESSER J H & DE TAKATS G (1941) *Arch Surg* Chicago 42 1 034
JEWELL P (1952) *J Anat Lond* 86 83
JIMENEZ DIAZ C BARREDA P DE LA MOLINA A F DE & ALCALA R (1954) *Circulation* 9 903
JOB C (1943) *Arch exp Path Pharmak* 202 633
JOELS N & SAMUELOFF M (1956) *J Physiol* 133 360
JONES J V (1952) *Brit J Pharmacol* 7 450
JONES J V (1953) *Brit J Pharmacol* 8 342
JONNESCO T & JONESCU D (1926) *Z ges exp med* 48 490
JOURDAN F & NOWAK S J G (1936) *Arch int Pharmacodyn* 53 121

KAHN R H (1930) *Z ges exp Med* 68 201
KAINDL F & EULER U S VON (1951) *Amer J Physiol* 166 284
KAINDL F WERNER G (1936) *Arch int Pharmacodyn* 76 457
KARASEK F (1933) *Arch int Physiol* 37 87
KARSNER H T (1911) *J exp Med* 14 322
KASTSCHENKO N (1887) *Arch mikr Anat* 30 1
KATZ B (1950) *J Physiol* 111 248 & 261
KATZENELBOGEN S & DE THURZO (1935) *Arch neurol Psych* 33 786
KAUFMANN P (1912) *Pflug arch ges Physiol* 146 231
KAUFMANN P (1912) *Pflug arch ges Physiol* 147, 35
KAZEM BECK — (1888) *Arch f Anat* 325
KAZEM BECK — (1902) *Anat Anz* 21 316
KELLEY R T FREIS E D & HIGGINS T F (1953) *Circulation* 7 169
KENNEY R A & NEIL E (1951) *J Physiol* 112 223
KENNEY R A NEIL E & SCHWEITZER A (1951) *J Physiol* 114 27
KETY S S & SCHMIDT C F (1945) *Amer J Physiol* 143 53
KETY S S & SCHMIDT C F (1948) *J clin Invest* 27 484
KEYS A B & BATEMAN J B (1932) *Biol Bull Woods Hole* 63 327
KEZDI P (1954) *Circulation Research* 2 367
KEZDI P (1953) *Arch intern Med* 91 26
KING A B (1939) *Bull Johns Hopkins Hosp* 65 489
KISCH B (1926) *Z ges exp Med* 52 499
KISCH B & SAKAI S (1923) *Pflug Arch ges Physiol* 198 65 86
KISCH B (1931) *Z Kreislforsch* 23 241
KLEMPERER E & WEISSMANN M (1932) *Jahrb Psych Neurol* 48 293
KLISIECKI A PICKFORD M ROTHSCHILD P & VERNEY E B (1933) *Proc roy Soc* B 112 521
KNOLL PH (1881) *Jb Lotos* (Prague) 2 34
KNOLL PH (1883) *S B Akad Wiss Wien* 88 479
KNOLL, PH (1885) *S B Akad Wiss Wien* 92 439 cited by Koch (1931)
KNOWLTON F P & STARLING E H (1912) *J Physiol* 44 206

KOCH E (1923) *Munch med Wschr* **70** 1316
KOCH E (1924) *Munch med Wschr* **70** 704
KOCH E (1929) *Z Kreisl Forsch* **22** 220
KOCH E (1929) *Z Kreisl Forsch* **21** 586
KOCH E (1931) *Die Reflektorische selbsteuerung des Kreislaufes* Steinkopff Leipzig
KOCH E (1932*a*) *Klin Wschr* **12** 225
KOCH E (1932*b*) *Z Kreisl Forsch* **24** 251
KOCH E & MARK R (1931) *Z Kreisl Forsch* **23** 319
KOCH E & MATTONET K (1934) *Z ges exp med* **94** 105
KOCH E (1927) *Z Kreisl Forsch* **19** 585
KOCH E & MIES H (1929) *Krankheitforschung* **7** 241
KOCH E MIES H & NORDMANN M (1927) *Z Kreisl Forsch* **19** 585
KOCH E & NORDMANN M (1928) *Z Kreisl Forsch* **20** 343
KOCH E & SIMON H (1928) *Klin Wschr* **7** 2 104
KOCH E & SIMON H (1929) *Z ges exp Med* **65** 594
KOELLE J B (1950) *J Pharmacol* **100** 158
KOESTER G & TSCHERMAK A (1902) *Arch Anat u Entwick* (Suppl) 255
KOESTER G & TSCHERMAK A (1903) *Pflug Arch ges Physiol* **93** 24
KOHN A (1899) *Ergebn Anat Entwgesch* **9** 194
KOHN A (1900) *Über den Bau und die Entwicklung der sog Carotisdruse* *Arch mikr Anat* **56** 81
KOPELMAN H & LEE G DE J (1951) *Clin Sci* **10** 383
KOSE W (1904) *Anat Anz* **25** 609
KOTTEGODA S R & MOTT J C (1955) *Brit J Pharmacol* **10** 66
KOWALEWSKY N & ADAMUEK E (1868) *Zbl med Wiss* **6** 545
KOYAMA S (1950) *Jap Circul J* **14** 228
KRAYER O & ACHESON G H (1946) *Physiol Rev* **26** 383
KRAYER O MOE G K & MENDEZ R (1944) *J Pharmacol* **82** 167
KRAYER O WOOD E H & MONTES G (1943) *J Pharmacol* **79** 215
KREIDMANN A (1878) *Anat Anz* 408
KREINDLER A (1946) *Bull Sec Scient Acad roumaine* **28** 448
KREMER M SCARFF R W & WRIGHT SAMSON (1933) *Brit J exp Pathol* **14** 281
KREMER M & WRIGHT SAMSON (1932) *Quart J exp Physiol* **21** 319
KREUZIGER H ASTEROTH H & LAMMERS L (1953) *Z ges exp Med* **120** 667
KROGH A (1912) *Skand Arch Physiol* **27** 126
KROGH A (1912) *Skand Arch Physiol* **27** 227
KROGH A (1941) *Comparative Physiology of Respiratory Mechanisms* Oxford Univ Press London
KROGH A & LEITCH I (1919) *J Physiol* **52** 288
KUBICEK W G (1953) *Amer J Physiol* **175** 380
KUNO Y & BRUCKE E T VON (1914) *Pflug Arch ges Physiol* **157** 117
KUNTZ A (1934) *The Autonomic Nervous System* Bailliere Tindall & Cox London
KUNTZ A (1945) *The Autonomic Nervous System* Lea & Febiger Philadelphia
KUSSMAUL A & TENNER A (1855) *Unters Naturl Mensch Tiere* **1** 90
KUSSMAUL A & TENNER A (1857) *Unters Naturl Mensch Tiere* **3** 1

LABORDE J V (1888) *Arch Physiol norm Path Ser* **4** **1** 397
LAMBERTSEN C J KOUGH R H COOPER D Y EMMEL G L LOESCHCKE H H & SCHMIDT C F (1953*a*) *J Appl Physiol* **5** 803 and 471
LAMBERTSEN C J STROUD M W GOULD R A EWING J H KOUGH R H & SCHMIDT C F (1953*b*) *J Appl Physiol* **5** 487
LANDGREN S (1952*a*) *Acta physiol scand* **26** 1
LANDGREN S (1952*b*) *Acta physiol scand* **26** 35
LANDGREN S LILJESTRAND G & ZOTTERMAN Y (1952) *Acta physiol scand* **26** 264
LANDGREN S LILJESTRAND G & ZOTTERMAN Y (1953) *Arch exp Path Pharmak* **219** 185
LANDGREN S LILJESTRAND G & ZOTTERMAN Y (1954) *Acta physiol scand* **30** 105
LANDGREN S LILJESTRAND G & ZOTTERMAN Y (1954) *Acta physiol scand* **30** 149
LANDGREN S & NEIL E (1951) *Acta physiol scand* **23** 152
LANDGREN S & NEIL E (1951) *Acta physiol scand* **23** 158
LANDGREN S & NEIL E (1952) *Acta physiol scand* **25** 286
LANDGREN S NEIL E & ZOTTERMAN Y (1952) *Acta physiol scand* **25** 24
LANDGREN S SKOUBY A P & ZOTTERMAN Y (1953) *Acta physiol scand* **29** 381

JACOBS M H (1920*a*) *Amer J Physiol* 51 321
JACOBS M H (1920*b*) *Amer J Physiol* 53 457
JACOBY M (1895) *Studien z Entwicklungsgeschichte der Halsorgane der Saugethiere und des Menschen* Inaug Diss Berlin
JANSEN W H TAMS W ACHELIS H (1924) *Dtsch Arch Klin Med* 144 1
JARISCH A (1925) *J Physiol* 60 419
JARISCH A (1928) *Dtsch med Wschr* 54 1171 and 1211
JARISCH A (1938) *Wien Klin Wschr* 51 1
JARISCH A (1940) *Arch Kreislforsch* 7 260
JARISCH A (1940) *Arch Kreislforsch* 9 1
JARISCH A (1941) *Klin Wschr* 20 1 045
JARISCH A (1941) *Arch exp Path Pharmak* 197 266
JARISCH A (1949) *Wien klin Wschr* 61 555
JARISCH A & HEUZE C (1937) *Arch exp Path Pharmak* 187 706
JARISCH A LANDGREN S NEIL E & ZOTTERMAN Y (1952) *Acta physiol scand* 25 195
JARISCH A & LUDWIG W (1926) *Arch exp Path Pharmak* 114 240
JARISCH A & RICHTER H (1939*a*) *Klin Wschr* 18 185
JARISCH A & RICHTER H (1939*b*) *Arch exp path Pharmak* 193 347
JARISCH A & RICHTER H (1939*c*) *Arch exp Path Pharmak* 193 355
JARISCH A & ZOTTERMAN Y (1948) *Acta physiol scand* 16 31
JESSER J H & DE TAKATS G (1941) *Arch Surg* Chicago 42 1 034
JEWELL P (1952) *J Anat Lond* 86 83
JIMENEZ DIAZ C BARREDA P DE LA MOLINA A F DE & ALCALA R (1954) *Circulation* 9 903
JOB C (1943) *Arch exp Path Pharmak* 202 633
JOELS N & SAMUELOFF M (1956) *J Physiol* 133 360
JONES J V (1952) *Brit J Pharmacol* 7 450
JONES J V (1953) *Brit J Pharmacol* 8 342
JONNESCO T & JONESCU D (1926) *Z ges exp med* 48 490
JOURDAN F & NOWAK S J G (1936) *Arch int Pharmacodyn* 53 121

KAHN R H (1930) *Z ges exp Med* 68 201
KAINDL F & EULER U S VON (1951) *Amer J Physiol* 166 284
KAINDL F WERNER G (1936) *Arch int Pharmacodyn* 76 457
KARASEK F (1933) *Arch int Physiol* 37 87
KARSNER H T (1911) *J exp Med* 14 322
KASTSCHENKO N (1887) *Arch mikr Anat* 30 1
KATZ B (1950) *J Physiol* 111 248 & 261
KATZENELBOGEN S & DE THURZO (1935) *Arch neurol Psych* 33 786
KAUFMANN P (1912) *Pflug arch ges Physiol* 146 231
KAUFMANN P (1912) *Pflug arch ges Physiol* 147 35
KAZEM BECK — (1888) *Arch f Anat* 325
KAZEM BECK — (1902) *Anat Anz* 21 316
KELLEY R T FREIS E D & HIGGINS T F (1953) *Circulation* 7, 169
KENNEY R A & NEIL E (1951) *J Physiol* 112 223
KENNEY R A NEIL E & SCHWEITZER A (1951) *J Physiol* 114 27
KETY S S & SCHMIDT C F (1945) *Amer J Physiol* 143 53
KETY S S & SCHMIDT C F (1948) *J clin Invest* 27 484
KEYS A B & BATEMAN J B (1932) *Biol Bull Woods Hole* 63 327
KEZDI P (1954) *Circulation Research* 2 367
KEZDI P (1953) *Arch intern Med* 91 26
KING A B (1939) *Bull Johns Hopkins Hosp* 65 489
KISCH B (1926) *Z ges exp Med* 52 499
KISCH B & SAKAI S (1923) *Pflug Arch ges Physiol* 198 65 86
KISCH B (1931) *Z Kreislforsch* 23 241
KLEMPERER E & WEISSMANN M (1932) *Jahrb Psych Neurol* 49 293
KLISIECKI A PICKFORD M ROTHSCHILD P & VERNEY E B (1933) *Proc roy Soc* B 112 521
KNOLL PH (1881) *Jb Lotos* (Prague) 2 34
KNOLL PH (1883) *S B Akad Wiss Wien* 88 479
KNOLL PH (1885) *S B Akad Wiss Wien* 92 439 cited by Koch (1931)
KNOWLTON F P & STARLING E H (1912) *J Physiol* 44 206

MALMÉJAC J (1934) *C R Soc Biol Paris* **116**, 532
MANDELSTAMM M ZAITSCHIK A JITNIKOFF B ELLENBOGEN O & SCHAFFRAM A (1929) *Arch Mal Coeur* **22** 457
MARCHAND F (1891) *Festschrift fur Virchow* Vol 1 p 537 Berlin
MAREY E J (1881) *La circulation du Sang* Masson Paris
MARGUTH H MARGUTH F & RAULE W (1951) *Arch int Pharmacodyn* **87** 17
MARGUTH H RAULE W & SCHAEFER H (1952) *Pflug Arch ges Physiol* **254** 224
MARINESCO G & KREINDLER A (1930) *Klin Wschr* **9** 2 204
MARINESCO G & KREINDLER A (1931) *J Physiol Path gen* **29** 77
MARK K E & NEUMANN H (1931) *Z ges exp Med* **80** 150
MARMORSTEIN M (1929) *J Physiol Path gen* **27** 762
MARMORSTEIN M (1933) *J Physiol Path gen* **31** 734
MARMORSTEIN M KOULIK N & LOUKATSCHER M (1934) *J Physiol Path gen* **32** 1 128
MARRI R & HAUSS W (1939) *Arch int Pharmacodyn* **63** 449
MARSHALL A M (1893) *Vertebrate Embryology* Smith Elder & Co London
MARSHALL E K & ROSENFELD M (1936) *J Pharmacol* **57** 437
MARTIN C J & LEPPER E H (1926) *Biochem J* **20** 107
MARTINI L & CALLIAUW L (1955) *Arch int Pharmacodyn* **101** 49
MARTINI L & ROVATI V (1954) *Arch int Pharmacodyn* **97** 4_0
MATHISON G C (1911) *J Physiol* **42** 283
MATTHEWS B H C (1931) *J Physiol* **71** 64
MATTHEWS B H C (1933) *J Physiol* **78** 1
MATTON G (1954) *J Physiol* **126** 13P
MATTON G (1957) *Arch int Pharmacodyn* **110** 471
MAURER F (1899) *Morph Jb* **27** 119
MAXIMOW A A & BLOOM W (1937) *Textbook of Histology* Saunders London
MAYER (1833) *Über ein neuengedecktes Ganglion im Winkel der ausseren und inneren carotis beim Menschen und Sangetieren (Ganglion intercaroticum)* See Mayer (1865)
MAYER S (1865) *Über das Ganglion intercaroticum* Inaug Diss Tubingen
MAYER S (1876) *S B Akad Wiss Wien* **74** 302
MAZZELLA H & MIGLIARO E (1949) *Arch int Pharmacodyn* **80** 79
MAZZELLA H WANG S C HEYMANS C & VLEESCHHOUWER G R DE (1951) *Arch int Pharmacodyn* **89** 122
MCCUBBIN J W GREEN J H & PAGE I H (1956*a*) *Circ Research* **4** 205
MCCUBBIN J W GREEN J H SALMOIRAGHI G C & PAGE I H (1956*b*) *J Pharmacol* **116** 191
MCDONALD R K & KELLEY V C (1948) *Amer J Physiol* **154** 201
MCDOWALL R J S (1924) *J Physiol* **59** 41
MCDOWALL R J S (1928) *Quart J exp Physiol* **18** 325
MCDOWALL R J S (1935*a*) *J Physiol* **84** 24P
MCDOWALL R J S (1935*b*) *J Physiol* **84** 56P
MCDOWALL R J S (1935*c*) *Physiol Rev* **15** 98
MCDOWALL R J S (1938) *The control of the circulation of the blood* Longmans Green London
MCDOWALL R J S (1950) *J Physiol* **111** 1
MCDOWALL R J S (1957) *The control of the circulation of the blood* Vol II Dawson London
MCINTOSH F C & PATON W D M (1949) *J Physiol* **109** 190
MCLAUGHLIN A I G (1933) *J Physiol* **80** 101
MCMICHAEL J (1937) *Quart J exp Physiol* **27** 55
MCMICHAEL J (1952) p 235 *Visceral Circulation* Ed G E W Wolstenholme Churchill London
MCNIDER W DE B (19_5) *South Med Surg* **87** 637
MCQUARRY I & SHOHL A T (1925) *J biol Chem* **66** 367
MCWILLIAM J A (1885) *J Physiol* **6** 192
MCWILLIAM J A (1890) *Brit med J* ii 948
MCWILLIAM J A (1933) *Quart J exp Physiol* **23** 1
MEEK W J (1941) *Physiol Rev* **21** 3_4
MEGIBOW R S KATZ L N & FEINSTEIN M (1943) *Arch intern Med* **71** 536
MEGIBOW R S KATZ & L N & STEINITZ F S (1942) *Surgery* **11** 19
MEHRMANN K (1925) *Der Heringsche Karotisdruckversuch beim Menschen* Inaug Diss Bonn
MEIJLING H A (1938) *Bau und Innervation von Glomus Caroticum und Sinus Caroticus* *Acta Neerl Morph* **1** 193
MELNIKOVA T A (1947) Cited by Anitchkov (1951)

MERCIER F RIZZIO C & DELPHAUT J (1934) *C R Soc Biol Paris* **115** 546
MERKLEN F P (1934) *Le sinus carotidien* Vigot Paris
MEURER H (1949) *Verh dtsch Ges Kreislaufforsch* 15 77
MEURERS K (1925) *Z ges exp Med* 46 135
MEYER F (1927) *Pflug Arch ges Physiol* **215** 545
MEYER H (1935) *Z vergl Physiol* 22 435
MEYER L (1876) *Arch Psychiat Nervenkr* 6 84
MICHAILOW S (1908) *Anat Anz* 32 87
MIES H (1932) *Z klin Med* **120** 613
MIESCHER RUSCH F (1885) *Arch Anat Physiol Lpz* 90 355
MIGUEL S MORA M & VIMA J (1946) *Trav Inst nac Cienc med Madr* 7 337
MILLER F R & BOWMAN G T (1915) *Amer J Physiol* 39 149
MILLER W S (1950) *The Lung* Thomas Springfield Ill
MILLS J N (1944) *J Physiol* **103** 244
MILLS T W (1885) *J Physiol* 5 359
MILLS T W (1885) *J Physiol* 6 246
MIZERES N J (1955) *Amer J Anat* 96 285
MOE G K BASSETT D L & KRAYER O (1944) *J Pharmacol* 80 272
MOE G K CAPO L R & PERALTA B R (1948) *Amer J Physiol* **153** 601
MOE G K & FREYBURGER W A (1950) *Pharmacol Rev* 2 61
MOE G K RENNICK B R CAPO L R & MARSHALL M R (1949) *Amer J Physiol* **157** 158
MOISSEJEFF E (1927) *Z ges exp Med* 53 696
MORAN N C DRESEL, P E PERKINS M E & RICHARDSON A P (1954) *J Pharmacol* **110** 415
MORAN N C PERKINS M E & RICHARDSON A P (1954) *J Pharmacol* 111, 454
MORRISON J L HEYMANS C RICHARDSON A P & WALKER H A (1951) *Arch int Pharmacodyn* 86 203
MORRISON R S (1935) *Amer J Physiol* **113** 229
MORUZZI G (1947) *Arch neerl physiol* 28 385
MOSCHCOWITZ E (1927) *Amer J med Sci* **174** 388
MOSSO A (1898) *Life of Man on the High Alps* Ch 22 Unwin London
MOTLEY H L COURNAND A WERKO L HIMMELSTEIN A & DRESDALE D (1947) *Amer J Physiol* **150** 315
MOTT J C (1950) *Proc zool Soc Lond* **120** 503
MOTT J C (1951) *J Physiol* **114** 387
MOTT J C & PAINTAL A S (1953) *Brit J Pharmacol* 8 238
MULINOS M G & SHULMAN I (1939) *Amer J Physiol* **125** 310
MURATORI G (1932) *Boll Soc ital Biol sper* 7 1
MURATORI G (1933) *Arch ital Anat Embriol* 30 573
MURATORI G (1934) *Boll Soc ital Biol sper* 9 1 041
MURATORI G (1934) *Arch ital Anat Embriol* 33 421
MURATORI G (1935) *Monit zool ital* 45 300
MURATORI G (1936) *Anat Anz* 83 367
MURATORI G (1937) *Arch ital Anat Embriol* 38 387
MURATORI G (1943) *Arch Ist Biochim ital* 15 145

NAKAO H BALLIN H M & GELLHORN E (1956) *Electroencephalog and Clin Neurophysiol* 8 413
NAKAYAMA S (1953) *J Physiol Soc Jap* 15 281
NAKAYAMA S (1953) *J Physiol Soc Jap* 15 290
NAKAYAMA S (1954) *Yonago Acta Medica* 1 110
NASH R A (1926) *J Physiol* 61 28P
NASHAT F S (1956) *Physiological Studies in Hypothermia* Ph D Thesis Univ of London
NASHAT F S & NEIL E (1955) *J Physiol* 127 59-60P
NATHANSON H M (1933) *Arch intern Med* 51 387
NATHANSON H M (1934) *Ibid* 54 111
NAUNYN B & SCHREIBER J (1881) *Arch exp Path Pharmak* 14 1
NAWALICHIN J (1870) *Zbl med Wiss* 8 483
NAWROCKI F (1874) *Beitr Anat Physiol als Festschriftgabe f C Ludwig* 205
NEIL, E (1951) *Acta physiol scand* 22 54
NEIL E (1954) p 44 in *Hypertension* Ed by G E W Wolstenholme and M P Cameron Churchill London

NEIL E (1954) *Arch Middlesex Hosp* **4** 16
NEIL E (1956*a*) *Arch int Pharmacodyn* **105** 468
NEIL E (1956*b*) *Arch int Pharmacodyn* **105** 477
NEIL E (1957) *Chemoreceptors and Circulation* Chapter in McDowall s Circulation of the Blood See ref McDowall (1957)
NEIL E REDWOOD C R M & SCHWEITZER A (1948) *J Physiol* **107** 8P
NEIL E REDWOOD C R M & SCHWEITZER A (1949*a*) *J Physiol* **109** 259
NEIL E REDWOOD C R M & SCHWEITZER A (1949*b*) *J Physiol* **109** 281
NEIL E REDWOOD C R M & SCHWEITZER A (1949*c*) *J Physiol* **109** 392
NEIL E STRÖM L & ZOTTERMAN Y (1950) *Acta physiol scand* **20** 338
NEIL E & ZOTTERMAN Y (1950) *Acta physiol scand* **20** 160
NELEMANS F A (1948) *Amer J Anat* **83** 43
NETTLESHIP W A (1936) *J comp Neurol* **64** 115
NEUBAUER J E (1772) *Descriptio anatomica cardiacorum nervorum* Hartung Jena p 75
NICKERSON M (1949) *Pharmacol Rev* **1** 27
NIDEN A H & AVIADO D M (1956) *Circ Research* **4** 67
NIELSEN M (1936) *Skand Arch Physiol* **74** Suppl 10
NIELSEN M & ASMUSSEN E (1953) *Ann Rev Physiol* **15** 85
NIELSEN M & HANSEN O (1937) *Skand Arch Physiol* **76** 37
NIELSEN M & SMITH H (1951) *Acta physiol scand* **24** 293
NIKOFOROWSKY P M (1912) *J Physiol* **45** 459
NITZESCU I I & JACOBOVICI I (1928) *Z ges exp Med* **63** 767
NONIDEZ J F (1935) *Anat Rec* **62** 47
NONIDEZ J F (1935) *Amer J Anat* **57** 259
NONIDEZ J F (1936) *J Anat Lond* **70** 215
NONIDEZ J F (1937) *Amer J Anat* **61** 203
NONIDEZ J F (1937) *Anat Rec* **69** 299
NONIDEZ J F (1939) *Amer J Anat* **65** 361
NONIDEZ J F (1941) *Amer J Anat* **68** 151
NONIDEZ J F (1943) *Amer Heart J* **26** 577
NORDENFELDT O (1941) *Acta med Scand* **108** Suppl 119
NORDMANN M (1929) *Krankheitsforschung* **7** 268
NOWAK S J G (1934) *C R Soc Biol Paris* **116** 642
NOWAK S J G (1938) *Arch int Pharmacodyn* **60** 118 and 129
NOWAK S J G (1940) *Ann Surg* **111** 102
NOWAK S J G & SAMAAN A (1935) *Arch int Pharmacodyn* **51** 463
NOWAK S J G & WALKER I J (1939) *New Engl J Med* **220** 269
NYLIN G (1934) *Skand Arch Physiol* **69** 237

OCHOTERENA I (1936) 1 *Anales Inst biol Univ Mexico* **7** 397
O CONNOR W J (1955) *Quart J exp Physiol* **40** 237
ODERMATT W (1923) *Dtsch Z Chir* **182** 341
OKAMURA C (1930) *Z ges Anat I Z Anat Entw Gesch* **92** 20
O LEARY J HEINBECKER P & BISHOP E H (1934) *Amer J Physiol* **109** 274
O LEARY J HEINBECKER P & BISHOP E H (1934) *Amer J Physiol* **109** 409
OLIVER G (1897) *J Physiol* **21** 22P
OLIVER G & SCHAFER E A (1895) *J Physiol* **18** 230
OLTHOFF H J (1934) *Z vergl Physiol* **21** 534
OSBORNE W A (1921) *J Physiol* **54** 100P
OSUGA R (1954) *Kyushu Mem Med Sci* **5** 1
OWSJANNIKOW Ph (1871) *Ber sachs Ges (Akad) Wiss* **23** 135

PAGANO G (1900) *Arch ital Biol* **33** 1
PAGE E B HICKAM J B SIEKER H O MCINTOSH H D & PRYOR W W (1955) *Circulation* **11** 262
PAGE I H MCCUBBIN J W & GREEN J H (1955) *Acta Cardiologica* **10** 576
PAINTAL A S (1953*a*) *J Physiol* **120** 596
PAINTAL A S (1953*b*) *J Physiol* **121** 182
PAINTAL A S (1953*c*) *J Physiol* **121** 341
PAINTAL A S (1953*d*) *J Physiol* **122** 181

PAINTAL A S (1954) *J Physiol* **126** 255
PAINTAL A S (1954) *J Physiol* **126** 276
PAINTAL A S (1955a) *Quart J exp Physiol* **40** 89
PAINTAL A S (1955b) *Quart J exp Physiol* **40** 348
PAINTAL, A S (1956) *Abstr Rev XX Internat Congress Physiol* 78
PALME F (1934) *Z mikr anat Forsch* **36** 391
PALME F (1935) *Anat Anz* **79** 288
PALME F (1936) *Z Kreisl Forsch* **28** 173
PALME F (1943) *Z ges exp Med* **113** 415
PALME F (1951) *Exp Med and Surg* **9** 404
PALTAUF R (1892) *Beitr path Anat* **2** 260
PANNIER R (1940) *Arch int Pharmacodyn* **64** 476
PANNIER R & BACKER J DE (1945) *Arch int Pharmacodyn* **70** 110
PARKER F & WEISS S (1936) *Amer J Path* **12** 573
PARIN V V (1947) *Amer J med Sci* **214** 167
PARRY C H (1799) *An inquiry into the symptoms and causes of the syncope anginosa commonly called angina pectoris* Cruttwell Bath
PARSONS T R & SHEARER C (1922) *J Physiol* **54** 62
PARTRIDGE R C (1935) *J Canad M A* **33** 11
PARTRIDGE R C (1939) *J Physiol* **96** 233
PATON W D M (1954) *Pharmacol Rev* **6** 59
PATON W D M & ZAIMIS E J (1952) *Pharmacol Rev* **4** 219
PAUNZ L (1923) *Virchows Arch* **241** 76
PAVLOV I P (1879) *Pflug Arch ges Physiol* **20** 210
PAVLOV I P (1895) *Proc Russian Med Soc* cited by Samaan (1934)
PAVLOV I P (1910) *The work of the digestive glands* 2nd ed Griffin London
PEARCE J W HENRY J P & CHAPMAN M (1956) *Abstr Proc XX Internat Congr Physiol* 711
PEARCE J W (1951) *Control of Pulmonary Blood Pressure and its Relation to Certain Reflex Respiratory Phenomena* D Phil Thesis (Oxford)
PEARCE J W & HENRY J P (1955) *Amer J Physiol* **183** 650
PEARCE J W & WHITTERIDGE D (1951) *Quart J exp Physiol* **36** 177
PENITSCHKA W (1930) *Med Klin* **26** 312
PENITSCHKA W (1931) *Z mikr anat Forsch* **24** 24
PERMAN E (1924) *Z ges Anat I Z Anat EntwGesch* **71** 382
PERMAN E (1925) *Z ges Anat I Z Anat EntwGesch* **75** 263
PETERS J P BULGER H A & EISENMAN A J (1924) *J biol Chem* **58** 747
PFLUGER E W F (1868) *Pflug Arch ges Physiol* **1** 61
PHILIPPEAU A (1885) *C R Soc Biol Paris* **37** 1
PHILIPPOT E (1937) *Arch int Pharmacodyn* **57** 357
PHILIPPOT E & DALLEMAGNE M J (1949) *Arch int Pharmacodyn* **80** 451
PICKERING G W KISSIN M & ROTHSCHILD P (1936) *Clin Sci* **2** 193
PILCHER & SOLLMANN T (1915) *J Pharmacol* **7** 295
PINOTTI O & GRANATA L (1954) *Boll Soc ital Biol sper* **30** 486
PINOTTI O & GRANATA L (1955) *Arch Sci biol Napoli* **39** 59
PISCHINGER A (1934) *Z Ges Anat I Z Anat EntwGesch* **103** 547
PI SUNER A (1947) *Physiol Rev* **27** 1
PITTS R F LARRABEE M G & BRONK D W (1941) *Amer J Physiol* **134** 359
PLECHKOVA E K (1936) *Bull Biol med exp URSS* **1** 402
PLUMIER L (1904) *J Physiol Path gen* **6** 655
PORTER R W (1954) *Recent Progr Hormone Res* **10** 1
PORTER W T & BEYER H G (1900) *Amer J Physiol* **4** 283
PORTER W T & PRATT J H (1908) *Amer J Physiol* **21** 16P
PORTER W T & PRATT J H (1914) *Amer J Physiol* **33** 373 431
POURFOUR DU PETIT (1727) *Mem de L Acad des sci* pp 1–19
PREISENDORF P (1880) *Dtsch Arch klin Med* **27** 387
PRENANT A (1896) *Cellule* **10** 87
PTASZEK L (1927) *C R Soc Biol Paris* **96** 567

QUINCKE, H (1875) *Dtsch klin Wschr* 189

RABL H (1922) *Arch mikr Anat* 96 315
RAHN H (1955) *Ann Rev Physiol* 17 107
RAHN H & BAHNSON H T (1953) *J Appl Physiol* 6 105
RAHN H BAHNSON H T MUXWORTHY J F & HAGEN J M (1953) *J Appl Physiol* 6 154
RAHN H & OTIS A B (1949) *Amer J Physiol* 157, 145
RASHKIND W J LEWIS D H HENDERSON J B HEIMAN D F & DIETRICK D B (1953) *Amer J Physiol* 175 415
RECHT G (1924) *Klin Wschr* 3 916
REGNIERS P (1930*a*) *Arch int Pharmacodyn* 39 371
REGNIERS P (1930*b*) *Rev Belg Sci méd* 2 207
REIN H (1931) *Ergebn Physiol* 32 28
REIN H & RÖSSLER R (1929) *Z Biol* 89 245
RHOADS C P VAN SLYKE D D HILLER A & ALVING A S (1934) *Amer J Physiol* 110 392
RICHARDS A N & WOODS W G (1915) *Amer J Physiol* 39 54
RICHARDSON A P WALKER H A FARRAR C B GRIFFITH W POUND E & DAVIDSON Y R (1952) *Proc Soc exp Biol N Y* 79 79
RICHTER H & AMANN A (1940) *Arch exp Path Pharmak* 196 275
RICHTER H & THOMA H (1939) *Arch exp Path Pharmak* 193 622
RIEGELE L (1928) *Z Anat I Z Anat EntwGesch* 86 142
RIJLANT P (1936) *C R Soc Biol Paris* 123 99
RIJNDERS H (1933) *Acta brev Neerl Physiol* 3 22
RILEY R L & HOUSTON C S (1951) *J Appl Physiol* 3 526
RIML O (1929) *Arch exp Path Pharmak* 139 240
RITCHIE W T (1912) *Quart J Med* 6 47
ROBERTS Ff (1924) *J Physiol* 59 99
ROBERTSON J D SWANN A A B & WHITTERIDGE D (1956) *J Physiol* 131 463
RODBARD S REYES M MININNI G & SAIKI H (1954) *Amer J Physiol* 176 341
RODBARD S & SAIKI H (1952) *Amer J Physiol* 168 234
RODBARD S & STONE W (1955) *Circulation* 12 883
ROEVER G (1869) *Krit und exp Unters d s Nerveinflusses auf die Erweiterung und Verenderung der Blutgefässe* p 71 Koch Rostock
ROMEIS B (1926) *Z ges Anat I Z Anat EntwGesch* 80 547
ROSENTHAL J (1862) *Hermanns Handb d Physiol* Vol 4 part 2 p 157 Vogel Leipzig
ROSENTHAL T B (1948) *J biol Chem* 173 25
ROSKAM J (1930) *Syncopes cardiaques graves et syncopes répétées par hyper reflectivité sino carotidienne Presse Méd* 38 590
ROSSI L (1930) *Cuore e Circul* 14 529
ROTHLIN L (1923) *Arch int Pharmacodyn* 27 459
ROTHLIN E & CERLETTI A (1954) *Schweiz med Wschr* 84 137
ROTHLIN E & KONZETT H (1954) *Arch int Pharmacodyn* 97 468
ROUGHTON F J W (1954) p 51 *in Handbook of Respy Physiology* U S A F Project 21-2301-0003
RUDBERG T (1938) *Skand Arch Physiol* 79 8
RUDBERG T (1940) *Acta physiol scand* 1 89

SAALFELD F VON (1933) *Pflüg Arch ges Physiol* 231 33
SAALFELD F VON (1933) *Pflüg Arch ges Physiol* 231 724
SABATIER A (1873) *Études sur le coeur et la circulation central dans la série des vertébrés* Coulet Montpellier
SAMAAN A (1934) *Ann Physiol Physicochim biol* 10 912
SAMAAN A (1935) *J Physiol* 83 313
SAMAAN A & STELLA G (1935) *J Physiol* 85 309
SANCETTA S M LYNN R B SIMEONE F A & SCOTT R W (1952) *Circulation* 6 559
SARKAR B B (1922) *Proc roy Soc* B 93 230
SASSA K & MIYAZAKI H (1920) *J Physiol* 54 203
SATO H (1954) *Tohoku J exp Med* 59 343
SCHAEFER H (1943) *Klin Wschr* 22 553
SCHAEFER H (1950) *Ergebn Physiol* 46 71
SCHAEFER H (1952) *Acta neuroveg* 4 201
SCHAEFER — (1877) *Allg Z Psychiat* 34 438
SCHAFER E A & SCHARLIEB H J (1904) *Trans Roy Soc Edinb* 41 311

SCHAFER E S (1919) *Quart J exp Physiol* 12 231
SCHAFER E S (1920) *Quart J exp Physiol* 12 373
SCHAFER P W (1944) *Surg Gynec Obstet* 79 163
SCHAPER A (1892) *Arch mikr Anat* 40 287
SCHAPIRO L (1881) *Dtsch Arch Klin Med* 27 132
SCHARF R (1925) *Pflug Arch ges Physiol* 207 65
SCHMIDT C F (1928) *Amer J Physiol* 84 202
SCHMIDT C F (1932) *Amer J Physiol* 102 94
SCHMIDT C F (1932) *Amer J Physiol* 102 119
SCHMIDT C F (1934) *Amer J Physiol* 110 137
SCHMIDT C F (1940) *J Lab clin Med* 26, 223
SCHMIDT C F (1940) *Anæsthesia and Analgesia* 19, 261
SCHMIDT C F (1941) Chapter on Respiration in McLeod s *Physiology in Modern Medicine* ed P Bard 9th edition Kimpton London
SCHMIDT C F (1944) *Anæsthesiology* 5 77
SCHMIDT C F (1945) *Ann Rev Physiol* 7 231
SCHMIDT C F (1950) *The Cerebral Circulation in Health and Disease* Thomas Springfield Ill
SCHMIDT C F (1956) Chapter on Respiration in McLeod s *Medical Physiology* ed P Bard 10th edition Kimpton London
SCHMIDT C F & COMROE J H (1940) *Physiol Rev* 20 115
SCHMIDT C F & COMROE J H (1941) *Ann Rev Physiol* 3 151
SCHMIDT C F & DRIPPS R D (1939) *Proc Soc exp Biol N Y* 42 31
SCHMIDT C F DUMKE P L & DRIPPS R D (1939) *Amer J Physiol* 128 1
SCHMIDT C F & HENDRIX J P (1938) *Proc Ass Res Nerv Ment Dis* 18 229
SCHMIEDEBERG O (1871) *Ber sachs Ges (Akad) Wiss* 23 152
SCHMITERLOW C G (1948) *Acta physiol scand* 16 suppl 56
SCHNEIDER E C (1931) *Amer J Physiol* 97 353
SCHNEIDER J A & YONKMAN F F (1953) *Amer J Physiol* 174 127
SCHNEIDER R (1950) *Anat An* 97 189
SCHNEIDER R (1951) *Z mikr anat Forsch* 57 104
SCHNEYER K (1935) *Pflug Arch ges Physiol* 235 176
SCHUMACHER S v (1902) *S B Akad Wiss Wien* 91 211
SCHUMACHER S v (1902) *Anat An* 21 1
SCHUMACHER S v (1915) *Arch mikr Anat* 87 309
SCHUMACHER S (1938) *Z mikr anat Forsch* 43 107
SCHURAWLEW A N (1928) *Z ges Anat I Z Anat EntwGesch* 86 730
SCHWEITZER A (1934) *Z Kreisl Forsch* 26 601
SCHWEITZER A (1935) *Klin Wschr* 665
SCHWEITZER A (1935b) *Verhl dtsch Ges Kreislaufforsch* 8 148
SCHWEITZER A (1936) *J Physiol* 87 46P
SCHWEITZER A (1937) *Die Irradiation autonomer Reflexe* Karger Basle
SCHWEITZER A (1945) *J Physiol* 104 25P
SCHWEITZER A (1950) *Cardiologia* 16 353
SCHWEITZER A & WRIGHT SAMSON (1937) *J Physiol* 88 459
SCHWEITZER A & WRIGHT SAMSON (1937) *J Physiol* 89 165
SCHWEITZER A & WRIGHT SAMSON (1937) *J Physiol* 90 310
SCHWEITZER A & WRIGHT SAMSON (1938a) *J Physiol* 92 422
SCHWEITZER A & WRIGHT SAMSON (1938b) *Quart J exp Physiol* 28 33
SCHWIEGK H (1935) *Pflug Arch ges Physiol* 236 206
SCOTT J M D (1925) *J Physiol* 59 443
SCOTT J C REED E A SARIS D & RAMIREZ H P R (1948) *Amer J Physiol* 154 428
SEITZ J F & ENGELHARDT W A (1949) *C R Acad Sci U R S S* 66 439
SELKURT E E (1953) *Amer J Physiol* 172 700
SELLADURAI S & WRIGHT SAMSON (1932) *Quart J exp Physiol* 22 233 and 285
SETO H (1935) *Z Zellforsch* 22 213
SEWALL H & DONALDSON F (1882) *J Physiol* 3 357
SEWALL H & STEINER D W (1885) *J Physiol* 6 162
SHARPEY SCHAFER E P & WALLACE J (1942) *Brit med J* 2 304
SHAW DUNN J (1919) *Quart J Med* 13 129
SHEN T C R & HAUSS W H (1939) *Arch int Pharmacodyn* 63 251

SHIMIZU K (1948) *Rinsho Geka (Clinical Surgery)* **3** 377
SHUMAN C R LEARNER N & DOANE J H (1954) *Amer Heart J* **47** 737
SICILIANO — (1900) *Arch ital Biol* **33** 338
SIEKER H O GAUER O H & HENRY J P (1954) *J clin Invest* **33** 572
SISSON G CAIN A & ROOT W S (1955) *Amer J Physiol* **180** 485
SJOSTRAND T (1952) *Acta physiol scand* **26** 312
SKWORZOW J (1874) Quoted by Anufriew (1928)
SMIRNOW G (1886) *Zbl med Wiss* **24** 145
SMIRNOW A (1895) *Anat An* **10** 737
SMIRNOW A (1900) *Anat An* **18** 105
SMIRNOW A I (1924) *Pflug Arch ges Physiol* **205** 687
SMIRNOW A I (1935) *Arch Sci biol St Petersb* **37** 231
SMITH C (1924) *Amer J Anat* **34** 87
SMITH G G & PORTER W T (1915) *Amer J Physiol* **38** 108
SMITH H W (1951) *The Kidney* Oxford University Press New York
SMYTH D H (1937) *J Physiol* **88** 425
SNYDER C D (1915) *Amer J Physiol* **37** 104
SOLLMANN T & BROWN E D (1912*a*) *Amer J Physiol* **30** 88
SOLLMANN T & BROWN E D (1912*b*) *Amer J Physiol* **30** 102
SOLLMANN T & PILCHER J D (1912) *Amer J Physiol* **30** 303 and 369
SPALITTA M F & CONSIGLIO M (1892) *Arch ital Biol* **17** 43
SPALITTA M F & CONSIGLIO M (1897) *Arch ital Biol* **28** 231
SPERANSKY N I & POPOW V G (1936) *J Physiol Path gen* **34** 477
SPYCHALA V (1933) *Z KreislForsch* **25** 730
SSINELNIKOW R (1928) *Z Anat I Z Anat EntwGesch* **86** 563
STADIE W C & MARTIN K A (1924) *J biol Chem* **61** 523
STARLING E H (1925) *Brit med J* **2** 1163
STELLA G (1931) *J Physiol* **73** 45
STELLA G (1933) *J Physiol* **77** 68
STELLA G (1935) *Quart J exp Physiol* **25** 145
STELLA G (1936) *J Physiol* **87** 78
STELLING C (1867) *Exp Untersuch uber den Einfluss des Nervus depressor auf die Herztatigkeit und den Blutdruck* Inaug Diss Laakman Dorpat
STERNBERG H & TAMARI M (1928) *Arch exp Path Pharmak* **136** 34
STEWART G N (1909) *Amer J Physiol* **24** 341
STEWART G N (1911) *Heart* **3** 77
STEWART G N PIKE F H & GUTHRIE F H (1908) *Amer J Physiol* **21** 359
STIEDA L (1881) *Untersuchungen uber di Entwicklung der Glandula thymus Glandula thyreoidea und Glandula Carotica* Engelmann Leipzig
STILLING B (1840) *Physiologische Pathologische und Medi inischpraktische Untersuchungen uber die Spinal Irritation p* 164 Wignand Leipzig
STILLING H (1899) *Anat An* **15** 229
STRAUB H (1926) *Z ges exp Med* **53** 197
STRAUSS E (1940) *Arch Kreislaufforsch* **6** 65
STROUD R C (1953) *J Appl Physiol* **6** 151
STUTZMANN J W MAISON G L & KUSSEROW G W (1949) *Proc soc exp biol N Y* **71** 725
STUTZMANN J W SIMON H & MAISON G L (1951) *J Pharmacol* **101** 310
SUNDER PLASSMANN P (1930) *Z ges Anat I Z Anat Entwgesch* **93** 567
SUNDER PLASSMANN P (1933) *Z ges Neurol Psych* **147** 414
SUTTON D C & LUETH H C (1930) *Arch intern Med* **45** 827
SVITZER E (1863) *Einige Untersuchungen uber das G intercaroticum* Thiele Kopenhagen Cited by S Mayer
SWAN A A B & WHITTERIDGE D *Abstr Comm XX Internat Congress Physiol* 867
SWISS E D & MAISON G L (1952) *J Pharmacol* **105** 87
SZEPSENWOL J (1935) *C R Soc Biol Paris* **119** 13
SZEPSENWOL J (1935) *C R Soc Anat 30th Reunion* 469

TAKAYASHU M (1908) *Acta Soc ophth jap* **12** 554
TAKINO M (1932) *Acta Sch med Univ Kioto* **15** 303 308 321
TAKINO M (1951) *Nippon J clin Angiocardiol* **15** 1 *In Biol Abstr* **26** 3608

TAKINO M & MIYAKE S (1936) *Acta Sch med Univ Kioto* **18** 226
TAKINO M & WATANABE S (1938) *Arch Kreislaufforsch* **11** 18
TAUBE H W L (1743) *De vera nervi intercostalis origine* Diss Inaug Vandenhoeck Gottingen Cited by Jacoby
TAYLOR C (1941) *Amer J Physiol* **135** 27
TAYLOR R D & PAGE I H (1951) *Circulation* **4** 184 563
TAYLOR R D PAGE I H & CORCORAN A C (1951) *Arch intern Med* **88** 1
TCHERNIGOVSKY V N (1954) *A propos des mecanismes de régulation du tonus vasculaire* 31 pp Moscow
TELLO J F (1922) *Trab Lab Invest biol Univ Madrid* **19** 89
TELLO J F (1924) *Trab Lab Invest biol Univ Madrid* **22** 295
TERNI T (1927) *Arch ital Anat Embriol* **24** 407
TERNI T (1931) *Z Anat I Z Anat EntwGesch* **96** 289
THIRY A (1864) *Zbl med Wiss* **2** 722
THOMAS C B (1944) *Johns Hopk Hosp Bull* **74**, 335
THOMAS C B & BROOKS C M (1935) *Amer J Physiol* **113** 130P
THOMAS C B & WARTHIN T A (1940) *Amer Heart J* **19** 316
THORN G W CLINTON M DAVIS B M & LEWIS R A (1945) *Endocrinology* **36** 381
TIGERSTEDT R (1921) *Die Physiologie des Kreislaufes* Vol 2 De Gruyter Berlin and Leipzig
TIGERSTEDT R (1923) *Die Physiologie des Kreislaufes* Vol 4 De Gruyter Berlin and Leipzig
TIITSO M (1937) *Pflug Arch ges Physiol* **238** 738
TIITSO M & TOOTSON E (1935) *Pflug Arch ges Physiol* **236** 251
TOH C C (1954) *J Physiol* **126** 248
TORRANCE R W & HOLMES R (1955) *J Physiol* **130** 45P
TORRANCE R W & WHITTERIDGE D (1948) *J Physiol* **107** 6P
TOURNADE A (1913) *C R Soc Biol Paris* **74** 956
TOURNADE A (1929) *C R Soc Biol Paris* **100** 1025
TOURNADE A (1930) *Lyon méd* **146** 97
TOURNADE A (1932) *C R Soc Biol Paris* **109** 879
TOURNADE A (1936) *C R Soc Biol Paris* **121** 910
TOURNADE A & CHABROL M (1921) *C R Soc Biol Paris* **84** 608
TOURNADE A & CHABROL M (1924) *C R Soc Biol Paris* **90** 835
TOURNADE A & CHABROL M (1924) *C R Soc Biol Paris* **91** 176
TOURNADE A & CHABROL M (1926) *C R Soc biol Paris* **94** 1199
TOURNADE A CHABROL M & MARCHAND H (1921) *C R Soc Biol Paris* **84** 610
TOURNADE A HERMANN H & JOURDAN F (1929) *C R Soc Biol Paris* **100** 1025
TOURNADE A & MALMEJAC J (1929) *C R Soc Biol Paris* **100** 708
TOURNADE A & MALMEJAC J (1930) *C R Soc Biol Paris* **105** 834
TOURNADE A & MALMEJAC J (1932) *C R Soc Biol Paris* **109** 1128
TOURNADE A & MALMEJAC J (1933) *C R Soc Biol Paris* **114** 1247
TRAUBE J (1862) *Allg med Zent Ztg* No 38 297
TRAUBE J (1863) *Ibid* No 97 769
TRAUBE J (1865) *Zbl med Wiss* **3** 881
TRENDELENBURG P (1923) *Ergebn Physiol* **21** 535
TRINCI G (1909) *Monit zool ital* **20** 286
TRINCI G (1912) *Arch ital Anat Embriol* **10** 197
TSCHERMAK J N (1866) *Jena Z Med Naturw* **2** 384
TSCHERMAK J N (1868) *Prag Vischr fd prakt Heilkr* **4** 30
TSCHERNJACHIWSKY A (1929) *Trav Lab Invest biol Univ Madrid* **26** 75
TSCHERNJACHIWSKY A. (1938) *C R Acad Sci U R S S* **8** 193
TSCHIRWINSKY S (1895) *Zbl Physiol* **9**, 777

UEDA H (1948) *Jap Circul J* **12** 64 Cited by Nakayama
UEDA H (1950) *Jap Circul J* **14** 149 Cited by Nakayama
URBAN H (1933) *Dtsch med Wschr* **59** 1597
UVNAS B (1954) *Physiol Rev* **34** 608

VALENTIN G (1833) *Über das Ganglion intercaroticum Wissenschaftl Annalen der gesammten Heilkunde von J F C Hecker* **26** (cited by S Mayer)

VAN DAM L (1938) *On the utilization of oxygen and the regulation of breathing in some aquatic animals* Volharding Groningen
VAN DER LINDEN P (1933) *Arch int Pharmacodyn* **46** 63
VAN DER LINDEN P (1934) *Arch int Physiol* **40** 59
VAN LOO A SURTSHIN A & KATZ L N (1948) *Amer J Physiol* **154** 397
VAN SLYKE D D RHOADS C P HILLER A & ALVING A (1934) *Amer J Physiol* **109** 336
VELLUDA C (1927) *Rec Med vet* **103** 139
VELLUDA C (1927b) *Arch Anat Strasbourg* **7** 323
VELLUDA C (1928–9) *Arch Anat Strasbourg* **9** 227
VERBEKE R (1949a) *Arch int Pharmacodyn* **79** 1
VERBEKE R (1949b) *Arch int Pharmacodyn* **80** 19
VERBEKE R & VLEESCHHOUWER G R DE (1950) *Arch int Pharmacodyn* **81** 1
VERBEKE R & VOTAVA Z (1949) *Arch int Pharmacodyn* **79** 367
VERCAUTEREN E (1932) *Arch int Pharmacodyn* **42** 339
VERDONK A (1939) *Arch int Pharmacodyn* **63** 376
VERDONK A (1941) *Arch int Pharmacodyn* **65** 111
VERDUN P (1898) *Derives branchiaux che les Vertebres superieures* Lagarde and Sebille Toulouse
VIALLI M & ERSPAMER V (1933) *Z Zellforsch* **19** 743
VIERORDT K (1855) *Die Lehre vom Arterienpuls in gesunden und kranken Zustanden* Vieweg Brunswick p 68
VILLARET M JUSTIN BESANCON L & BARDIN P (1936) *Bull Soc med Hop Paris* 840 936 941
VOLHARD F (1948) *Schwei med Wschr* **78** 1 189
VULPIAN A (1856) *C R Acad Sci Paris* **43** 663

WADA MASANORI (1952) *J Kurume Med Ass* **15** 99
WAKERLIN G E CRANDALL E FRANK M H JOHNSON D POMPER L & SCHMID H E (1954) *Circ Research* **2** 416
WALKER H A JONES P S & RICHARDSON A P (1953) *J Pharmacol* **109** 301
WALKER H A WILSON S FARRAR C & RICHARDSON A P (1952) *J Pharmacol* **104** 211
WALKER H A WILSON S HEYMANS C & RICHARDSON A P (1950) *Arch int Pharmacodyn* **82** 395
WALLER A (1853) *C R Acad Sci Paris* **36** 381
WALLER A (1862) *Proc Roy Soc* B **11** 302
WALSH E G (1947) *J Physiol* **106** 446
WALTER F (1877) *Arch exp Path Pharmak* **7** 148
WANG S C & BORISON H L (1947) *Amer J Physiol* **150** 712 and 722
WANG S C MAZZELLA H & HEYMANS C (1952) *Arch int Pharmacodyn* **90** 1
WANG S C NGAI S H & GROSSMAN R G (1954) *J Pharmacol* **110** 51
WANG S C VLEESCHHOUWER G R DE PANNIER R & DELAUNOIS A L (1950) *Arch int Pharmacodyn* **83** 149
WARBURG E J (1922) *Biochem J* **16** 153
WARD R O (1908) *J Physiol* **37** 378
WATT J G DUMKE P R & COMROE J H (1943) *Amer J Physiol* **138** 610
WATZKA M (1934) *Anat An* **78** 108
WATZKA M (1937) *Z ges Anat I Z Anat EntwGesch* **108** 61
WATZKA M (1943) p 262 in *Handbuch der mikr Anat des Menschen* (ed W Mollendorff) *Vol VI/4*
WEBER E (1911) *Arch Anat Physiol Lp (physiol Abt) Jahrgang* 1910 *Suppl* 377
WEBER E F (1846) *Handworterbuch d Physiologie* **II** 45
WEBER E F & WEBER E H (1845) *Annalie Universali di Medicina* **116** 223
WEBER E H (1831) *Hildebrandt s Handbuch d Anat 4th Edition Part III* p 75
WEISS S & BAKER J (1933) *Medicine* **12** 297
WEISS S CAPPS R B FERRIS E B & MUNRO D (1936) *Arch intern Med* **58** 407
WENCKEBACH K F & WINTERBERG H (1927) *Über die unregelmassige Her tatigkeit* Leipzig
WERKO L BIORCK G CRAFOORD C WULFF G KROOK H & ELIASCH H (1953) *Amer Heart J* **45** 477
WESTCOTT R N FOWLER N O SCOTT R C HANENSTEIN V D & MCGUIRE J (1951) *J clin Invest* **30** 957
WESTERLUND A (1906) *Skand Arch Physiol* **18** 263
WHITE E G (1935) *Beitr path Anat* **96** 177
WHITE J C GARREY W E & ATKINS J A (1933) *Arch Surg Chicago* **26** 765

WHITEHORN W V EDELMANN A & HITCHCOCK F A (1946) *Amer J Physiol* 146 61
WHITTERIDGE D (1948) *J Physiol* 107 107
WHITTERIDGE D (1948) *J Physiol* 107 496
WHITTERIDGE D (1950) *Physiol Rev* 30 475
WHITTERIDGE D (1953) *Visceral circulation* ed G E W Wolstenholme Churchill London p 123
WHITTERIDGE D (1953) *Abstr Comm XIX Congr Physiol* 66
WHITTERIDGE D & BULBRING E (1944) *J Pharmacol* 81 340
WHITTERIDGE D & BÜLBRING E (1946) *Brit med Bull* 4 85
WIESEL J (1906) *Wien Klin Wschr* 19 723
WIGGERS C J (1949) *Physiology in Health and Disease 5th edn* Kimpton London
WILKINS R W DOUPE J & NEWMAN H W (1938) *Clin Sci* 3 403
WILLMER E N (1934) *J exp Biol* 11 283
WILMOTH P & LEGER L (194_) *Le sinus carotidien* Masson Paris
WINDER C V (1933) *Amer J Physiol* 106 28
WINDER C V (1937) *Amer J Physiol* 118 379
WINDER C V (1938) *Amer J Physiol* 122 306
WINDER C V (1938) *Amer J Physiol* 123 217
WINDER C V (1938) *Amer J Physiol* 124 421
WINDER C V (1939) *Amer J Physiol* 126 P655
WINDER C V (1942) *Amer J Physiol* 136 200
WINDER C V BERNTHAL, T & WEEKS W F (1938) *Amer J Physiol* 124 238
WINDER, C V & WINDER H O (1933) *Amer J Physiol* 105 337
WINDER C V WINDER H O & GESELL R (1933) *Amer J Physiol* 105 311
WINIWARTER H DE (1934) *C R Ass Anat 29e Reunion Bruxelles* 519
WINIWARTER H DE (1939) *Arch Biol* (Paris) 50 67
WINTERSTEIN H (1911) *Pflug Arch ges Physiol* 138 167
WINTERSTEIN H (1915) *Bioch Z* 70 45
WINTERSTEIN H (1921) *Pflug Arch ges Physiol* 187 293
WINTERSTEIN H (1949) *Experientia* 5 221
WINTERSTEIN H (1952) *Pflug Arch ges Physiol* 256 96
WINTERSTEIN H (1953) *Acta Physiol Latinoamer* 3 195
WINTERSTEIN H (1955) *Ergebn Physiol* 48 328
WINTERSTEIN H (1956) *New Engl J Med* 255 216 272 331
WINTERSTEIN H & GOKHAN N (1953) *Arch int Pharmacodyn* 93 363
WITZLEB E (1952) *Pflug Arch ges Physiol* 256 234
WITZLEB E (1953) *Pflug Arch ges Physiol* 257 244
WITZLEB E BARTELS H BUDDE H & MOCHIZUCKI M (1955) *Pflug Arch ges Physiol* 261 211
WOLHYNSKI F A (1937) *Anat An* 83 261
WOLHYNSKI T (1928) *Z ges Anat I Z Anat EntwGesch* 86 608
WOOD H C (1902) *Amer J Physiol* 6 283
WOOD P (1952) *Brit Med Bull* 8 348
WOOD P (1956) *Abstr Comm IInd European Congress Cardiology*
WOOLDRIDGE L (1883) *Arch Anat Physiol Physiol Abt* 522
WOOLLARD H H (1926) *J Anat Lond* 60 345
WOROBIEW W P (1917) *Zur Topographie d Nervenstamme und Ganglien des Her ens beim Menschen* Kharkov
WRIGHT SAMSON (1930*a*) *J Physiol* 69 331
WRIGHT SAMSON (1930*b*) *J Physiol* 69 493
WRIGHT SAMSON (1932) *Brit med J* 1 457
WRIGHT SAMSON (1934) *Quart J exp Physiol* 24 169
WRIGHT SAMSON (1937) *Quart J exp Physiol* 26 63
WRIGHT SAMSON (1938) *Quart J exp Physiol* 28 33

YAMADA S & BURTON A C (1954) *J Appl Physiol* 6 501

ZAIMIS E J (1955) *J Pharmacol* 7 497
ZANCHETTI A. WANG S C & MORUZZI G (1952) *Electroenceph clin Neurophysiol* 4 357
ZBYSZEWSKY L (1928) *C R Soc Biol Paris* 99 1 040
ZIMMERMAN W (1887) *Über die Carotidendruse von R esculenta* Inaug Diss Berlin
ZOTTERMAN Y (1935) *Acta physiol scand* 72 73

ZOTTERMAN Y (1944) *Acta physiol scand* **8** 377
ZOTTERMAN Y (1948) *Nord Med* *38* 1 182
ZOTTERMAN Y (1953) *Abstr Comm XIX Internat Congress Physiology* p 59
ZUNTZ N LOEWY A MULLER F CASPARI W (1906) *Hohenklima und bergwanderungen* Bong Berlin
ZUNZ E & TREMONTI P (1931) *Arch int Pharmacodyn* **40** 449
ZUNZ E & TREMONTI P (1931) *Arch int Pharmacodyn* **41** 1

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